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Non-absorbable disaccharides versus placebo/no intervention and lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis (Review)

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[Intervention Review]

Non-absorbable disaccharides versus placebo/no intervention and lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis

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ABSTRACT

Background

Non-absorbable disaccharides (lactulose and lactitol) are recommended as first-line treatment for hepatic encephalopathy. The previous (second) version of this review included 10 randomised clinical trials (RCTs) evaluating non-absorbable disaccharides versus placebo/no intervention and eight RCTs evaluating lactulose versus lactitol for people with cirrhosis and hepatic encephalopathy. The review found no evidence to either support or refute the use of the non-absorbable disaccharides and no differences between lactulose versus lactitol.

Objectives

To assess the beneficial and harmful effects of i) non-absorbable disaccharides versus placebo/no intervention and ii) lactulose versus lactitol in people with cirrhosis and hepatic encephalopathy.

Search methods

We carried out electronic searches of the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 10), MEDLINE, EMBASE, and Science Citation Index Expanded to 19 October 2015; manual searches of meetings and conference proceedings; checks of bibliographies; and correspondence with investigators and pharmaceutical companies.

Selection criteria

We included RCTs, irrespective of publication status, language, or blinding.

Data collection and analysis

Two review authors, working independently, retrieved data from published reports and correspondence with investigators. The primary outcomes were mortality, hepatic encephalopathy, and serious adverse events. We presented the results of meta-analyses as risk ratios (RR) and mean differences (MD) with 95% confidence intervals (CI). We assessed the quality of the evidence using 'Grading of Recommendations Assessment Development and Evaluation' (GRADE) and bias control using the Cochrane Hepato-Biliary Group domains. Our analyses included regression analyses of publication bias and other small study effects, Trial Sequential Analyses to detect type 1 and type 2 errors, and subgroup and sensitivity analyses.

Main results

We included 38 RCTs with a total of 1828 participants. Eight RCTs had a low risk of bias in the assessment of mortality. All trials had a high risk of bias in the assessment of the remaining outcomes. Random-effects meta-analysis showed a beneficial effect of non-absorbable disaccharides versus placebo/no intervention on mortality when including all RCTs with extractable data (RR 0.59, 95% CI 0.40 to 0.87; 1487 participants; 24 RCTs; I^2 = 0%; *moderate quality evidence*) and in the eight RCTs with a low risk of bias (RR 0.63, 95% CI 0.41 to 0.97; 705 participants). The Trial Sequential Analysis with the relative risk reduction (RRR) reduced to 30% confirmed the findings when including all RCTs, but not when including only RCTs with a low risk of bias or when we reduced the RRR to 22%. Compared with placebo/no intervention, the non-absorbable disaccharides were associated with beneficial effects on hepatic encephalopathy (RR 0.58, 95% CI 0.50 to 0.69; 1415 participants; 22 RCTs; I^2 = 32%; *moderate quality evidence*). Additional analyses showed that non-absorbable disaccharides can help to reduce serious adverse events associated with the underlying liver disease including liver failure, hepatorenal syndrome, and variceal bleeding (RR 0.47, 95% CI 0.36 to 0.60; 1487 participants; 24 RCTs; I^2 = 0%; *moderate quality evidence*). We confirmed the results in Trial Sequential Analysis. Tests for subgroup differences showed no statistical differences between RCTs evaluating prevention, overt, or minimal hepatic encephalopathy. The evaluation of secondary outcomes showed a potential beneficial effect of the non-absorbable disaccharides on quality of life, but we were not able to include the data in an overall meta-analysis (*very low quality evidence*). Non-absorbable disaccharides were associated with non-serious (mainly gastrointestinal) adverse events (*very low quality evidence*). None of the RCTs comparing lactulose versus lactitol evaluated quality of life. The review found no differences between lactulose and lactitol for the remaining outcomes (*very low quality evidence*).

Authors' conclusions

This review includes a large number of RCTs evaluating the prevention or treatment of hepatic encephalopathy. The analyses found evidence that non-absorbable disaccharides may be associated with a beneficial effect on clinically relevant outcomes compared with placebo/no intervention.

PLAIN LANGUAGE SUMMARY

Are non-absorbable disaccharides associated with beneficial or harmful effects in people with cirrhosis and hepatic encephalopathy?

Background

Cirrhosis is a chronic disorder of the liver. People with cirrhosis may develop hepatic encephalopathy, a condition that results in poor brain functioning. Hepatic encephalopathy may be clinically obvious (*overt*) with changes including poor concentration, tremor, and alterations in consciousness. Others have no obvious clinical changes (minimal) but, when tested, some aspects of brain function such as attention and the ability to perform complex tasks are impaired.

The reason why people develop hepatic encephalopathy is complex. The accumulation of ammonia plays a key role. The non-absorbable disaccharides, lactulose and lactitol, are indigestible sugars that reduce the levels of ammonia in the blood.

Review question

We investigated the use of non-absorbable disaccharides for the prevention and treatment of hepatic encephalopathy in people with cirrhosis by reviewing randomised clinical trials (RCTs).

Search date

The search date was October 2015.

Study funding sources

Seven RCTs received financial support and 11 RCTs received lactitol or inactive placebo free of charge from a pharmaceutical company.

Study characteristics

We included 29 RCTs comparing non-absorbable disaccharides with inactive placebo or no intervention and nine RCTs comparing lactulose with lactitol. Seven of the included RCTs evaluated the prevention of hepatic encephalopathy and 31 evaluated the treatment of hepatic encephalopathy. Sixteen of the treatment RCTs included people with *overt* hepatic encephalopathy while 15 included people with *minimal* hepatic encephalopathy. The duration of treatment varied depending on the type of hepatic encephalopathy from five days to one year.

Key results

People who received non-absorbable disaccharides were less likely to die than people given a placebo or no treatment. They were also less likely to develop serious complications of their liver disease such as liver failure, bleeding, and infections. The non-absorbable disaccharides were also effective in preventing the development of hepatic encephalopathy and increased the number of participants who recovered from hepatic encephalopathy. There was some evidence from a small number of trials that lactulose has a beneficial effect

on the quality of life, but we were unable to include the data in an overall analysis. The non-absorbable disaccharides were associated with adverse events including diarrhoea, nausea, bloating, and flatulence. None of the RCTs comparing lactulose versus lactitol reported quality of life. The analyses showed no differences between the two interventions for the remaining outcomes.

Quality of the evidence

In the comparison of non-absorbable disaccharides versus placebo/no intervention, we found moderate quality evidence of benefit for the outcomes of death, hepatic encephalopathy, and serious complications. The evidence for the remaining outcomes was of very low quality.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Non-absorbable disaccharides versus placebo/no intervention for the prevention and treatment of hepatic encephalopathy in people with cirrhosis

Non-absorbable disaccharides versus placebo/no intervention for the prevention and treatment of hepatic encephalopathy in people with cirrhosis

Population: prevention and treatment of hepatic encephalopathy in people with cirrhosis
Intervention: non-absorbable disaccharides (lactulose and lactitol)
Control: placebo/no intervention

Setting: in-hospital (overt hepatic encephalopathy) and outpatient (minimal hepatic encephalopathy and prevention trials)

Duration of follow-up: the duration depended on the type of encephalopathy with 5 days for acute, 74 days for chronic, 70 days for minimal, and 207 days for prevention of hepatic encephalopathy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Non-absorbable disaccharides versus placebo/no intervention				
Mortality	**Study population**		**RR 0.59** (0.40 to 0.87) when including all RCTs; **RR 0.63** (0.41 to 0.97) when including RCTs with a low risk of bias	1487 (24 studies)	⊕⊕⊕⊖ **moderate** [1]	**Trial Sequential Analysis:** The Trial Sequential Analysis found a beneficial effect of the intervention including all RCTs, but when the analysis only included RCTs with a low risk of bias. **Assessment method:** Assessed based on the total number of participants who died.
	88 per 1000	**49 per 1000** (32 to 75)				
	Moderate					
	20 per 1000	**11 per 1000** (7 to 17)				
Hepatic encephalopathy	**Study population**		**RR 0.58** (0.5 to 0.69)	1415 (22 studies)	⊕⊕⊕⊖ **moderate** [2]	**Trial Sequential Analysis:** The Trial Sequential Analysis found a beneficial effect of the intervention including all RCTs, but when the analysis only included RCTs with a low risk of bias.
	469 per 1000	**272 per 1000** (234 to 323)				
	Moderate					

	423 per 1000	**245 per 1000** (211 to 292)				**Assessment method:** Assessed based on the definitions in included RCTs (number of participants without a clinically relevant improvement of hepatic encephalopathy).
Serious adverse events	**Study population**		**RR 0.47** (0.36 to 0.6)	1487 (24 studies)	⊕⊕⊕⊖ **moderate** [3]	**Trial Sequential Analysis:** The Trial Sequential Analysis found a beneficial effect of the intervention including all RCTs, but when the analysis only included RCTs with a low risk of bias. **Assessment method:** Assessed and defined as any untoward medical occurrence that led to death, was life threatening, or required hospitalisation or prolongation of hospitalisation (ICH-GCP 2007).
	207 per 1000	**97 per 1000** (75 to 124)				
	Moderate					
	142 per 1000	**67 per 1000** (51 to 85)				
Quality of life (secondary outcome)		No overall estimate available			⊕⊖⊖⊖ **very low** [4]	We were unable to combine the data into an overall analysis due to unacceptably high heterogeneity. **Assessment method:** Based on the quality of life questionnaires.
Non-serious adverse events (secondary outcome)	**Study population**		**RR 2.47** (1.24 to 4.93)	739 (9 studies)	⊕⊖⊖⊖ **very low** [5]	**Assessment method:** The outcome includes all adverse events that do not fulfil the criteria for 'serious' (ICH-GCP 2007).
	106 per 1000	**261 per 1000** (131 to 521)				
	Moderate					
	63 per 1000	**156 per 1000** (78 to 311)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised clinical trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Mortality is downgraded one level to '*moderate quality evidence*' because the Trial Sequential Analysis found insufficient evidence when we limited the analysis to include only RCTs with a low risk of bias.

[2]Hepatic encephalopathy is downgraded one level to '*moderate quality evidence*' because none of the RCTs had a low risk of bias in the overall assessment.
[3]Serious adverse events is downgraded one level to '*moderate quality evidence*' because none of the RCTs had a low risk of bias in the overall assessment.
[4]Quality of life is downgraded three levels to '*very low quality evidence*' because i) none of the included RCTs had a low risk of bias, ii) the heterogeneity was considerable, and iii) we were unable to combine the data in an overall analysis.
[5]Non-serious adverse events is downgraded three levels to '*very low quality evidence*' because i) none of the included RCTs had a low risk of bias, ii) the confidence intervals were wide (uncertainty), and iii) we were only able to include data from nine RCTs in our meta-analysis.

Summary of findings 2. Lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis

Lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis

Population: prevention and treatment of hepatic encephalopathy in people with cirrhosis
Intervention: lactulose
Control: lactitol

Setting: in-hospital (overt hepatic encephalopathy) and outpatient (minimal hepatic encephalopathy and prevention trials)

Duration of follow-up: the duration depended on the type of encephalopathy with 5 days for acute, 74 days for chronic, 70 days for minimal, and 207 days for prevention of hepatic encephalopathy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Lactulose versus lactitol				
Mortality	**Study population**		**RR 1.3** (0.59 to 2.85)	225 (8 studies)	⊕⊖⊖⊖ **very low** [1]	**Trial Sequential Analysis:** The Trial Sequential Analysis found no evidence to support or refute a difference between the 2 interventions being compared. **Assessment method:** Assessed based on the total number of participants who died.
	71 per 1000	**92 per 1000** (42 to 202)				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Hepatic encephalopathy	**Study population**		**RR 1** (0.84 to 1.19)	194 (7 studies)	⊕⊖⊖⊖ **very low** [1]	**Trial Sequential Analysis:** The Trial Sequential Analysis found no evidence to support or refute a difference between the 2 interventions being compared.
	286 per 1000	**286 per 1000** (240 to 340)				
	Moderate					

	200 per 1000	**200 per 1000** (168 to 238)				**Assessment method:** Assessed based on the definitions in included RCTs (number of participants without a clinically relevant improvement of hepatic encephalopathy).
Serious adverse events	**Study population**		**RR 1.56** (0.84 to 2.88)	245 (9 studies)	⊕⊖⊖⊖ **very low** [1]	**Trial Sequential Analysis:** The Trial Sequential Analysis found no evidence to support or refute a difference between the 2 interventions being compared. **Assessment method:** Assessed based on the definitions in included RCTs (number of participants without a clinically relevant improvement of hepatic encephalopathy.
	106 per 1000	**165 per 1000** (89 to 304)				
	Moderate					
	77 per 1000	**120 per 1000** (65 to 222)				
Quality of life (secondary outcome)	—	No data were available for this outcome	—	—	—	None of the included RCTs assessed quality of life.
Non-serious adverse events (secondary outcome)	**Study population**		**RR 1.55** (0.88 to 2.74)	169 (6 studies)	⊕⊖⊖⊖ **very low** [2]	**Assessment method:** The outcome includes all adverse events that do not fulfil the criteria for 'serious' (ICH-GCP 2007).
	247 per 1000	**383 per 1000** (217 to 677)				
	Moderate					
	246 per 1000	**381 per 1000** (216 to 674)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised clinical trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Mortality, hepatic encephalopathy, and serious adverse events are downgraded three levels to '*very low quality evidence*' because i) the Trial Sequential Analysis found insufficient evidence to support or refute a difference between the intervention and control group, ii) the confidence intervals were wide, and ii) none of the included RCTs had a low risk of bias in the overall assessment of bias control.
[2]Non-serious adverse events is downgraded three levels to '*very low quality evidence*' because i) none of the included RCTs had a low risk of bias in the overall assessment of bias control, ii) only six RCTs reported the outcome, and iii) the confidence intervals were wide (uncertainty).

BACKGROUND

Description of the condition

The term hepatic encephalopathy refers to a spectrum of neuropsychiatric changes occurring in people with liver disease. The joint guideline from the European and American Associations for the Study of the Liver defines hepatic encephalopathy as a brain dysfunction associated with liver insufficiency or portal systemic shunting (EASL and AASLD guideline 2014a; EASL and AASLD guideline 2014b). Clinically apparent or *overt* hepatic encephalopathy manifests as a neuropsychiatric syndrome encompassing a wide spectrum of mental and motor disorders (Weissenborn 1998; Ferenci 2002). Events such as gastrointestinal bleeding, infection, and alcohol misuse can trigger this so-called *acute* or *episodic* hepatic encephalopathy. Fifty per cent of instances occur with no obvious cause. Episodes may recur. Between episodes, people may return to their baseline neuropsychiatric status or show clinical evidence of impairment (Bajaj 2010b). Less frequently, people present with *persistent* neuropsychiatric abnormalities, which are always present to some degree, but may vary in seriousness. Often people with persistent abnormalities have extensive spontaneous portal-systemic shunting or else a surgically created or transjugular intrahepatic portosystemic shunt (TIPS).

Changes in *mental state* range from subtle alterations in personality, intellectual capacity, and cognitive function to more profound alterations in consciousness leading to deep coma with decerebrate posturing. The changes in *motor function* may include rigidity, disorders of speech production, resting- and movement-induced tremor, asterixis, delayed diadochocinetic movements, hyperreflexia, hyporeflexia, choreoathetoid movements, Babinsky's sign, and transient focal symptoms (Victor 1965; Weissenborn 1998; Cadranel 2001). *Asterixis* (flapping tremor) is the best known motor abnormality. Individuals with overt hepatic encephalopathy also show a wide spectrum of other abnormalities, including impaired psychometric performance (Schomerus 1998), disturbed neurophysiological function (Parsons-Smith 1957; Chu 1997), altered cerebral neurochemical/neurotransmitter homeostasis (Taylor-Robinson 1994), reductions in global and regional cerebral blood flow and metabolism (O'Carroll 1991), and changes in cerebral fluid homeostasis (Haussinger 2000). In general, the degree of impairment in these parameters increases as the clinical condition worsens. The term *minimal* hepatic encephalopathy (in the older literature *subclinical* or *latent*) refers to people with cirrhosis who are 'clinically normal', but who show abnormalities in neuropsychometric or neurophysiological performance (Ferenci 2002).

The diagnosis of hepatic encephalopathy may present no problems, but without the background information and an obvious precipitating event, it may go unrecognised. We have no gold standard for the diagnosis (Montagnese 2004), but techniques that we can use singly or in combination. The diagnosis or exclusion of overt hepatic encephalopathy should include a careful and detailed neuropsychiatric history and examination (Montagnese 2004), with particular attention paid to changes in memory, concentration, cognition, and consciousness. Clinicians and researchers often use the West Haven Criteria to grade mental state (Conn 1977), and the Glasgow Coma Score to grade the level of consciousness (Teasdale 1974). The neurological examination should be comprehensive, looking particularly for evidence of subtle motor abnormalities. The assessment should consider and exclude other potential causes of neuropsychiatric abnormalities including concomitant neurological disorders and metabolic abnormalities such as those associated with diabetes, renal failure, drug, or alcohol intoxication. People with hepatic encephalopathy have impaired psychometric performance (Montagnese 2004; Randolph 2009). Those with minimal hepatic encephalopathy show deficits in attention, visuo-spatial abilities, fine motor skills, and memory while their other cognitive functions are relatively well preserved. People with overt hepatic encephalopathy show additional disturbances in psychomotor speed, executive function, and concentration. Psychometric test batteries to assess cognitive function form part of the evaluation. The Psychometric Hepatic Encephalopathy Score has a high specificity for the diagnosis (Schomerus 1998; Weissenborn 2001). The test employs five paper and pencil tests to assess attention, visual perception and visuo-constructive abilities. Test scores have to be normalised to take account of factors such as age, gender, and educational level. At present, normative databases are available in Germany, Italy, Denmark, Spain, Mexico, Korea, India, and Great Britain.

People with hepatic encephalopathy may have a number of neurophysiological abnormalities (Guérit 2009). The electroencephalogram, which primarily reflects cortical neuronal activity, may show progressive slowing of the background activity and abnormal wave morphology. Recent advances in electroencephalogram analysis should provide better quantifiable and more informative data. Other potential diagnostic techniques include the Critical Flicker Fusion Frequency (Kircheis 2002), and the Inhibitory Control Test (Bajaj 2008). The tests need further validation. Studies using structural and functional cerebral imaging techniques have helped to unravel the pathophysiology of hepatic encephalopathy, but they currently offer little diagnostically (Grover 2006; Berding 2009).

Description of the intervention

The non-absorbable disaccharides lactulose and lactitol are poorly absorbed sugars, which act as osmotic laxatives in the treatment of constipation (Johanson 2007; Miller 2014). Lactulose (Montgomery 1929) is dispensed as a syrup, which is contaminated with other sugars; a pure crystalline preparation is also available. Lactitol, a second-generation disaccharide, is dispensed as a powder. The mode of administration is generally enteral.

How the intervention might work

The exact pathogenesis of hepatic encephalopathy is unknown. Ammonia plays a key role (Butterworth 2014). The main sources of ammonia include nitrogenous products in the diet, bacterial metabolism of urea and proteins in the colon, and deamination of glutamine in the small intestine. Non-absorbable disaccharides lower ammonia levels through a number of mechanisms: (i) *a laxative effect*: the colonic metabolism of lactulose and lactitol results in an increase in intraluminal gas formation, an increase in intraluminal osmolality, a reduction in intraluminal pH, and an overall decrease in transit time; (ii) *bacterial uptake of ammonia*: the intraluminal changes in pH result in a leaching of ammonia from the circulation into the colon. The colonic bacteria use the released volatile fatty acids as substrate and proliferate. In doing so, they use the trapped colonic ammonia as a nitrogen source for protein synthesis. The increase in bacterial numbers additionally 'bulks'

the stool and contributes to the cathartic effect; (iii) *reduction of intestinal ammonia production*: non-absorbable disaccharides inhibit glutaminase activity and interfere with the intestinal uptake of glutamine and its subsequent metabolism to ammonia; (iv) *beneficial effects on the gut microbiome:* cirrhosis is associated with dysbiosis and changes in the colonic mucosal microbiome (Qin 2014). Further changes may be observed in patients with hepatic encephalopathy(Bajaj 2012). Non-absorbable disaccharides can beneficially affect microbiota composition (Riggio 1990b; Bajaj 2012).

Why it is important to do this review

The prevalence of hepatic encephalopathy varies. About 10% to 14% have overt hepatic encephalopathy when first diagnosed with cirrhosis (Saunders 1981). In studies in people with decompensated cirrhosis, about 20% have overt hepatic encephalopathy (D'Amico 1986; de Jongh 1992; Zipprich 2012). The cumulated incidence of overt hepatic encephalopathy is as high as 40% (Randolph 2009; Bajaj 2011a). The prevalence of minimal hepatic encephalopathy varies in different studies, but it may be more than 50% or higher in people with previous overt hepatic encephalopathy (Sharma 2010; Lauridsen 2011). The presence of hepatic encephalopathy, whether minimal or overt, is associated with significant impairment in the performance of complex tasks, such as driving (Schomerus 1981; Bajaj 2009; Kircheis 2009). The condition is also associated with a detrimental effect on quality of life (Groeneweg 1998) and safety (Roman 2011). In addition, the presence of overt hepatic encephalopathy in people with cirrhosis awaiting liver transplantation has a detrimental effect on neurocognitive function following the procedure (Sotil 2009) and on overall survival (Bustamante 1999; D'Amico 2006; Stewart 2007; Bajaj 2011a; Patidar 2014). The survival probability in people with cirrhosis after their first episode of hepatic encephalopathy is 42% at one year and 23% at three years (Bustamante 1999). Thus, more than 50% die within one year and more than 75% within three years. Overt hepatic encephalopathy also poses a substantial burden for the caregivers of affected people (Bajaj 2011b), and a significant financial burden on healthcare systems (Poordad 2007; Stepanova 2012).

Since 1966 (Bircher 1966), when lactulose was first introduced into clinical practice, several RCTs have evaluated non-absorbable disaccharides for hepatic encephalopathy. Previous meta-analyses have found that lactitol may be more beneficial than lactulose (Blanc 1992), or that lactulose and lactitol had comparable effects (Camma 1993). The previous versions of this review did not find sufficient evidence to recommend lactulose or lactitol for routine clinical use in people with cirrhosis and hepatic encephalopathy (Als-Nielsen 2000; Als-Nielsen 2004a; Als-Nielsen 2004b; Als-Nielsen 2005). Methodological issues including unclear bias control and lack of statistical power weakened the strength of the conclusions. A subsequent guideline from the European and American Association for the Study of Liver Diseases recommended lactulose as the intervention of choice for overt hepatic encephalopathy and its secondary prevention after an index event (EASL and AASLD guideline 2014a; EASL and AASLD guideline 2014b). The guideline did not recommend primary prevention of encephalopathy nor the routine treatment of minimal hepatic encephalopathy. Clinicians may consider treating minimal hepatic encephalopathy on a case by case basis under certain circumstances such as impaired driving skills, work performance, quality of life issues, or cognitive impairment. The original Cochrane review and the current European and American Associations for the Study of the Liver guidelines provide discrepant views about the role of lactulose. We therefore conducted this updated review.

OBJECTIVES

To assess the beneficial and harmful effects of i) non-absorbable disaccharides versus placebo/no intervention and ii) lactulose versus lactitol in people with cirrhosis and hepatic encephalopathy.

To avoid overlap with another planned Cochrane review, we did not evaluate non-absorbable disaccharides versus antibiotics (Kimer 2015).

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs, regardless of publication status, language, or blinding.

Types of participants

We included people with cirrhosis from RCTs on the prevention (primary or secondary) or treatment of hepatic encephalopathy, regardless of sex, age, aetiology of the underlying liver disease, type of hepatic encephalopathy, or precipitating factors.

Types of interventions

The intervention comparisons were i) non-absorbable disaccharides (lactulose or lactitol) versus placebo/no intervention and ii) lactulose versus lactitol. We included RCTs, irrespective of the doses, treatment durations, and modes of administration and allowed co-interventions if administered equally to allocation trial arms.

Types of outcome measures

We assessed all outcomes at the maximum duration of follow-up (Gluud 2015).

Primary outcomes

1. Mortality.
2. Hepatic encephalopathy. We based our assessment of hepatic encephalopathy on the definitions in included RCTs.
3. Serious adverse events defined as any untoward medical occurrence that led to death, was life threatening, or required hospitalisation or prolongation of hospitalisation (ICH-GCP 2007). We analysed serious adverse events as a composite outcome (Gluud 2015).

Secondary outcomes

1. Quality of life.
2. Non-serious adverse events: all adverse events that did not fulfil the criteria for a serious adverse event.
3. Surrogate outcomes: Number Connection Test results and blood ammonia concentrations.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and Science Citation Index Expanded using the strategies described in Appendix 1. The last search update was 19 October 2015.

Searching other resources

We scanned the reference lists of relevant articles and proceedings from meetings of the British Society for Gastroenterology (BSG), the British Association for the Study of the Liver (BASL), the European Association for the Study of the Liver (EASL), the United European Gastroenterology Week (UEGW), the American Gastroenterological Association (AGA), the American Association for the Study of Liver Diseases (AASLD), and the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN). We wrote to the principal authors of RCTs and the pharmaceutical companies involved in the production of non-absorbable disaccharides for additional information about completed RCTs and for information about any ongoing RCTs, and searched the database ClinicalTrials.gov (clinicaltrials.gov/) and the World Health Organization (WHO) online trial meta-register (apps.who.int/trialsearch/).

Data collection and analysis

Selection of studies

Two review authors (Lise L Gluud and Marsha Y Morgan) read the electronic searches, performed additional manual searches, and listed potentially eligible RCTs. All authors read the potentially eligible trial reports and participated in the final selection of those to be included in the analyses. We reached the final selection through consensus. For RCTs reported in more than one publication, we selected the paper reporting the longest duration of follow-up as the primary reference. We listed details of all included RCTs (Characteristics of included studies) and excluded studies (Characteristics of excluded studies).

Data extraction and management

Two review authors (Lise L Gluud and Marsha Y Morgan) independently collected data and resolved contrary opinions through discussion. The collected data included information on: i) RCTs: design (cross-over or parallel), settings (number of clinical sites; outpatient or inpatient; inclusion period), country of origin; ii) participants: mean age, proportion of men, aetiology of cirrhosis, type of hepatic encephalopathy, previous history of hepatic encephalopathy and iii) interventions: type, dose, duration of therapy, mode of administration. We gathered the primary and secondary outcome data, including the criteria used in the assessment of hepatic encephalopathy, and bias control information. A commercial translation services or medical personnel fluent in the language translated foreign language (non-English) papers (Acknowledgements). We requested missing data and other information from authors of included RCTs.

Assessment of risk of bias in included studies

We assessed bias control using the domains described in the Cochrane Hepato-Biliary (CHB) module and classified the risk of bias for each domain as high, unclear, or low and the overall assessment as high or low (Gluud 2015).

Allocation sequence generation

- Low risk of bias: sequence generation achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, or throwing dice are adequate if performed by an independent person not otherwise involved in the trial.
- Unclear risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (for example, if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants, personnel, and outcome assessors

- Low risk of bias: blinding was performed adequately. We defined lack of blinding (detection and performance bias) as not likely to affect the assessment of the outcome mortality.
- Unclear risk of bias: there was insufficient information to assess whether blinding was likely to induce bias in the results.
- High risk of bias: no blinding or incomplete blinding, and the assessment of outcomes was likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. The investigators used sufficient methods, such as intention-to-treat analyses with multiple imputations or carry-forward analyses to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data induced bias in the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported clinically relevant outcomes (mortality, hepatic encephalopathy, and serious adverse events). If we had access to the original trial protocol, the outcomes selected were those called for in that protocol. If we obtained information from a trial registry (such as www.clinicaltrials.gov), we only used that information if the investigators registered the trial before inclusion of the first participant.

- Unclear risk of bias: not all pre-defined outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more predefined outcomes were not reported.

For-profit bias

- Low risk of bias: the trial was free of industry sponsorship or other type of for-profit support that may influence the trial design, conduct, or results.
- Unclear risk of bias: no information on clinical trial support or sponsorship was available.
- High risk of bias: the trial was sponsored by industry, received support in the form of lactulose, lactitol, or placebo, or received any other type of support.

Other bias

- Low risk of bias: the trial appeared to be free of other biases including: medicinal dosing problems or follow-up (as defined below).
- Unclear risk of bias: the trial may or may not have been free of other domains that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias such as the administration of inappropriate treatments being given to the controls (e.g. an inappropriate dose) or follow-up (e.g. the trial included different follow-up schedules for participants in the allocation groups).

Overall bias assessment

- Low risk of bias: all domains were low risk of bias using the definitions described above.
- High risk of bias: one or more of the bias domains were of unclear or high risk of bias.

Measures of treatment effect

We used risk ratios (RR) for dichotomous outcomes and the mean differences (MD) for continuous outcomes, both with 95% confidence intervals (CI). For primary outcomes, we calculated the number needed to treat to benefit (NNTB) as 1/ risk difference (RD) based on the highest quality evidence (RCTs with a low risk of bias where available).

Unit of analysis issues

We included data from the first treatment period of cross-over trials (Higgins 2011a).

Dealing with missing data

We extracted data on all randomised participants in order to allow intention-to-treat analyses. To evaluate the importance of missing data, we conducted a worst-case scenario analysis with simple imputation (Higgins 2008), with inclusion of missing outcomes as treatment failures. We also conducted an 'extreme' worst-case scenario analysis in which we included missing outcome data as treatment failures (intervention group) or successes (control group).

Assessment of heterogeneity

We expressed heterogeneity as I^2 values using the following thresholds: 0% to 40% (unimportant), 40% to 60% (moderate), 60% to 80% (substantial), and > 80% (considerable). This information is included in the 'Summary of findings' tables (GRADEpro).

Assessment of reporting biases

For meta-analyses with at least 10 RCTs, we assessed reporting biases through regression analyses using the Harbord test (Harbord 2006), which regresses Z/sqrt(V) against sqrt(V), where Z is the efficient score and V is Fisher's information (the variance of Z under the null hypothesis). All meta-analyses of continuous outcomes included fewer than 10 RCTs.

Data synthesis

We performed the analyses in Review Manager 5 (RevMan 2014), STATA (Stata), and Trial Sequential Analysis (Thorlund 2011; TSA 2011).

Meta-analysis

We undertook random-effects and fixed-effect meta-analyses. Although the conclusion of the two models concurred, the random-effects meta-analysis provides the most conservative estimate of intervention effects. Therefore, we report the random-effects meta-analyses in our results.

Trial Sequential Analysis

We performed a Trial Sequential Analysis (Higgins 2008; Thorlund 2011), and defined the required information size (also known as the *heterogeneity adjusted required information size*) as the number of participants needed to detect or reject an intervention effect based on the relative risk reduction (RRR) and CGR. The analyses show firm evidence if the Z-curve crosses the monitoring boundary (also known as the *trial sequential monitoring boundary*) before reaching the required information size. We constructed futility boundaries to evaluate the uncertainty of obtaining a chance negative finding and performed the analyses with alpha set to 5%, power to 80%, and model-based diversity. Based on previous evidence (Thorlund 2011; EASL and AASLD guideline 2014a; EASL and AASLD guideline 2014b), we set the relative risk reduction (RRR) to 30% and the CGR to 15% (mortality), 45% (hepatic encephalopathy), and 30% (serious adverse events). In the analysis of mortality, we conducted the analysis with inclusion of i) all RCTs and ii) RCTs with a low risk of bias (only possible in mortality analyses). We repeated the analyses with the RRR reduced to 20% and with diversity increased by 20% (from 0% to 20% in the analyses of mortality and serious adverse events and from 30% to 50% in the analysis of hepatic encephalopathy).

Subgroup analysis and investigation of heterogeneity

We undertook subgroup analyses to investigate the effect of non-absorbable disaccharides in RCTs evaluating the prevention or treatment of hepatic encephalopathy. We also evaluated heterogeneity based on stratification of RCTs by:

- primary or secondary prevention of hepatic encephalopathy;
- overt or minimal hepatic encephalopathy;
- acute or chronic hepatic encephalopathy.

Sensitivity analysis

We performed a sensitivity analysis including only RCTs with a low risk of bias (as described above) and worse-case scenario analysis as described above.

'Summary of findings' tables

We used the GRADE system to evaluate the quality of the evidence for outcomes reported in the review considering the within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimate, and risk of publication bias (GRADEpro).

RESULTS

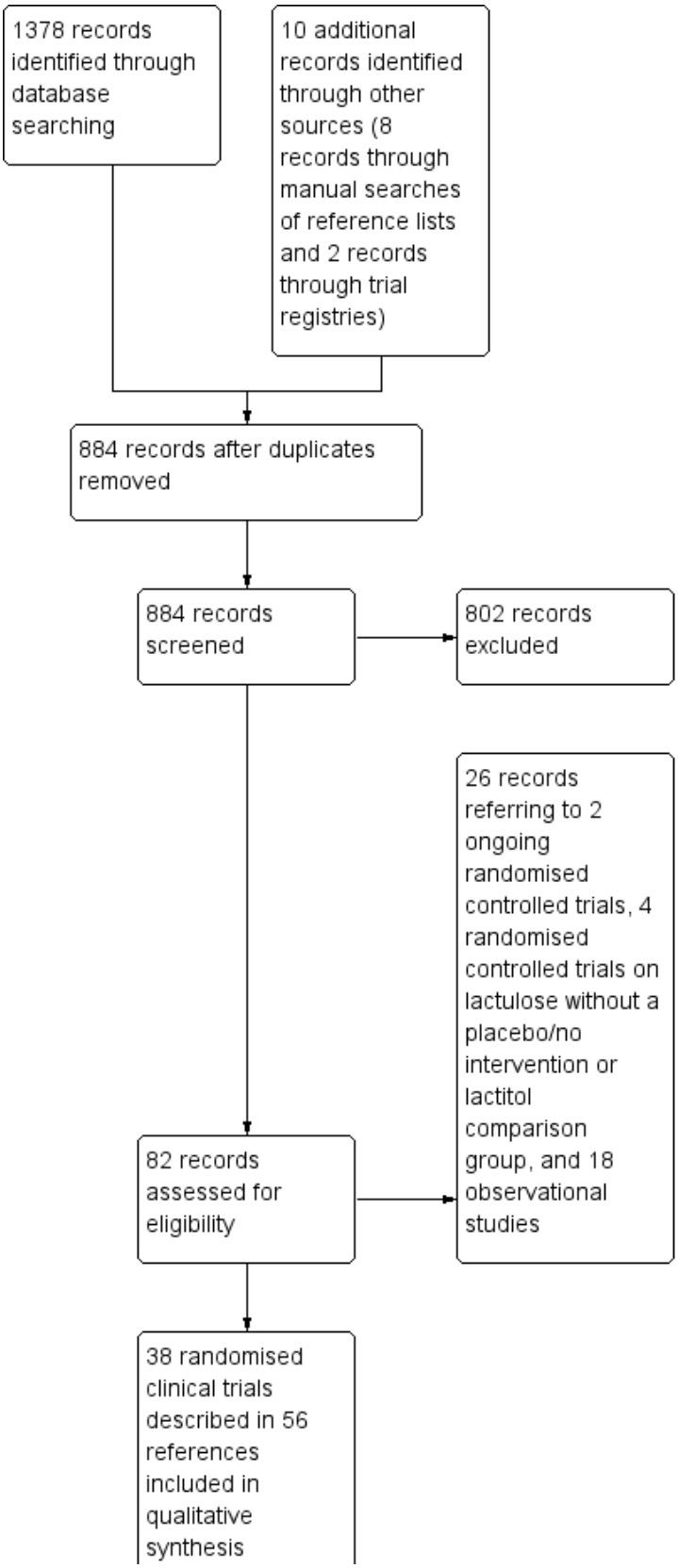
Description of studies

We included 38 RCTs in our qualitative analyses (Characteristics of included studies) and excluded 24 studies (Characteristics of excluded studies). We were able to gather data for our quantitative analyses from 34 RCTs.

Results of the search

We identified 1378 potentially relevant references in electronic databases and 10 additional records through manual searches (Figure 1). After removing duplicates and references that were clearly irrelevant, we identified 38 RCTs described in 56 references that fulfilled our inclusion criteria (Elkington 1969; Simmons 1970; Brown 1971; Germain 1973; Rodgers 1973; Corazza 1982; McClain 1984; Heredia 1987; Morgan 1987a; Morgan 1987b; Uribe 1987a; Uribe 1987b; Heredia 1988; Morgan 1989; Riggio 1989; Grandi 1991; Pai 1995; Jankovic 1996; Horsmans 1997; Quero 1997; Shi 1997; Watanabe 1997; Li 1999; Dhiman 2000; Xing 2003; Zeng 2003; Raza 2004; Riggio 2005; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013; Wen 2013; Ziada 2013; Yao 2014).

Figure 1. Trial flow diagram.



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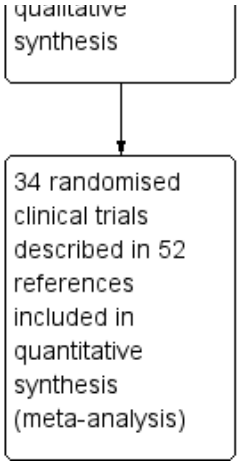


We were unable to obtain outcome data from four RCTs (Elkington 1969; Brown 1971; Rodgers 1973; Shi 1997), and we included the remaining 34 RCTs, all published as full paper articles, in our quantitative analyses (Simmons 1970; Germain 1973; Corazza 1982; McClain 1984; Heredia 1987; Morgan 1987a; Morgan 1987b; Uribe 1987a; Uribe 1987b; Heredia 1988; Morgan 1989; Riggio 1989; Grandi 1991; Pai 1995; Jankovic 1996; Horsmans 1997; Quero 1997; Watanabe 1997; Li 1999; Dhiman 2000; Xing 2003; Zeng 2003; Raza 2004; Riggio 2005; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013; Wen 2013; Ziada 2013; Yao 2014).

The countries of origin were India (Dhiman 2000; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013), the USA (Elkington 1969; Simmons 1970; Brown 1971; Rodgers 1973; McClain 1984), China (Shi 1997; Xing 2003; Zeng 2003; Wen 2013; Li 1999; Yao 2014), Italy (Corazza 1982; Riggio 1989; Grandi 1991; Riggio 2005), the United Kingdom (Morgan 1987a; Morgan 1987b; Morgan 1989), Spain (Heredia 1987; Heredia 1988), Mexico (Uribe 1987a; Uribe 1987b), Belgium (Horsmans 1997), Egypt (Ziada 2013), France (Germain 1973), Holland (Quero 1997), Pakistan (Raza 2004), Serbia (Jankovic 1996), and Taiwan (Pai 1995).

Included studies

Participants

The total number of participants was 1828. Their mean age ranged from 41 to 67 years and the proportion of men from 11% to 100%. The proportion of participants with cirrhosis secondary to hepatitis B/C infection ranged from 0% to 81%, while the proportion with alcohol-related cirrhosis ranged from 0% to 100%.

Seven RCTs evaluated the prevention of hepatic encephalopathy. Three RCTs evaluated primary (Sharma 2012), or secondary prevention of hepatic encephalopathy (Sharma 2009; Agrawal 2012), in participants with no obvious risks. Four included participants with an increased risk of hepatic encephalopathy due to gastrointestinal bleeding (Sharma 2011; Wen 2013), recent insertion of a transjugular intrahepatic portosystemic shunt (Riggio 2005), or portosystemic shunt surgery (Riggio 1989). In 16 RCTs, participants had *overt* hepatic encephalopathy (Table 1) classed as acute (Simmons 1970; Heredia 1987; Morgan 1987a; Uribe 1987a; Pai 1995; Jankovic 1996; Raza 2004), or chronic (Elkington 1969; Brown 1971; Germain 1973; Rodgers 1973; Corazza 1982; Morgan 1987b; Uribe 1987b; Heredia 1988; Grandi 1991). In 15 RCTs, participants had minimal hepatic encephalopathy (McClain 1984; Morgan 1989; Horsmans 1997; Quero 1997; Shi 1997; Watanabe 1997; Li 1999; Dhiman 2000; Xing 2003; Zeng 2003; Prasad 2007; Mittal 2011; Jain 2013; Ziada 2013; Yao 2014).

Interventions

Twenty-nine RCTs assessed non-absorbable disaccharides versus placebo/no intervention (Elkington 1969; Simmons 1970; Brown 1971; Germain 1973; Rodgers 1973; Corazza 1982; McClain 1984; Uribe 1987a; Uribe 1987b; Horsmans 1997; Quero 1997; Shi 1997; Watanabe 1997; Li 1999; Dhiman 2000; Xing 2003; Zeng 2003; Raza 2004; Riggio 2005; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013; Wen 2013; Ziada 2013; Yao 2014). Of these, 25 assessed lactulose (Elkington 1969; Simmons 1970; Brown 1971; Germain 1973; Rodgers 1973; Corazza 1982; McClain 1984; Horsmans 1997; Quero 1997; Watanabe 1997; Li 1999; Dhiman 2000; Xing 2003; Zeng 2003; Raza 2004; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013; Wen 2013; Ziada 2013; Yao 2014), and four assessed lactitol (Uribe 1987a; Uribe 1987b; Shi 1997; Riggio 2005).

Nine RCTs compared lactulose versus lactitol (Heredia 1987; Morgan 1987a; Morgan 1987b; Heredia 1988; Morgan 1989; Riggio 1989; Grandi 1991; Pai 1995; Jankovic 1996).

Outcomes

We were unable to extract outcome data from four RCTs with 64 participants (Elkington 1969; Brown 1971; Rodgers 1973; Shi 1997).

In total, our quantitative analyses included 34 RCTs with 1764 participants (Simmons 1970; Germain 1973; Corazza 1982; McClain 1984; Heredia 1987; Morgan 1987a; Morgan 1987b; Uribe 1987a; Uribe 1987b; Heredia 1988; Morgan 1989; Riggio 1989; Grandi 1991; Pai 1995; Jankovic 1996; Horsmans 1997; Quero 1997; Watanabe 1997; Li 1999; Dhiman 2000; Xing 2003; Zeng 2003; Raza 2004; Riggio 2005; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013; Wen 2013; Yao 2014).

Thirty-one RCTs followed participants to the end of the intervention (Simmons 1970; Germain 1973; Corazza 1982; McClain 1984; Heredia 1987; Morgan 1987b; Uribe 1987a; Uribe 1987b; Heredia

1988; Morgan 1989; Riggio 1989; Grandi 1991; Pai 1995; Horsmans 1997; Watanabe 1997; Li 1999; Dhiman 2000; Xing 2003; Zeng 2003; Raza 2004; Riggio 2005; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013; Wen 2013; Ziada 2013; Yao 2014). Three parallel-arm RCTs followed participants for an additional 13 days (Jankovic 1996), one month (Morgan 1987a), or three months after the end of treatment (Quero 1997). The duration of the intervention depended on the type of hepatic encephalopathy. Overall, the RCTs followed participants for 89 days (range 4 to 360 days) after randomisation. In prevention RCTs, the duration was 207 days (range 5 to 360 days). For participants with overt hepatic encephalopathy, the mean duration was 49 days (range 4 to 360) with a shorter duration in RCTs on acute (mean 5 days; range 4 to 7 days) and chronic hepatic encephalopathy (mean 74 days; range 10 to 360 days). The mean duration was 70 days in RCTs on minimal hepatic encephalopathy (range 14 to 180).

Investigators assessed overt (Table 1) and minimal hepatic encephalopathy using several different neuropsychiatric assessments and variables (Characteristics of included studies). Eight RCTs used the Portal Systemic Encephalopathy Index and Ratio (Morgan 1987a; Morgan 1987b; Uribe 1987a; Uribe 1987b; Heredia 1988; Riggio 1989; Pai 1995; Riggio 2005), which comprises mental status (West Haven Criteria), asterixis, Number Connection Test A results, blood ammonia concentrations, and the electroencephalogram mean cycle frequency. Two RCTs used a modified version of the test without the electroencephalogram (Grandi 1991; Raza 2004), while one additionally replaced Number Connection Test A with the Digit Symbol test (Raza 2004).

Ten of the remaining RCTs also used West Haven Criteria to assess mental status (Jankovic 1996; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013; Wen 2013; Ziada 2013). Three RCTs used the Conn Score, which is similar to the West Haven Criteria (Heredia 1987; Morgan 1989; Watanabe 1997). Thirty-two RCTs employed the Number Connection Test (Germain 1973; McClain 1984; Heredia 1987; Morgan 1987a; Morgan 1987b; Uribe 1987a; Uribe 1987b; Heredia 1988; Morgan 1989; Riggio 1989; Grandi 1991; Pai 1995; Jankovic 1996; Horsmans 1997; Quero 1997; Shi 1997; Watanabe 1997; Li 1999; Dhiman 2000; Xing 2003; Zeng 2003; Raza 2004; Riggio 2005; Prasad 2007; Sharma 2009; Mittal 2011; Agrawal 2012; Sharma 2012; Jain 2013; Wen 2013; Ziada 2013; Yao 2014). Twenty-five RCTs measured blood ammonia in plasma, venous, or arterial blood (Elkington 1969; Simmons 1970; Brown 1971; Germain 1973; Corazza 1982; Heredia 1987; Morgan 1987a; Morgan 1987b; Uribe 1987a; Uribe 1987b; Heredia 1988; Riggio 1989; Grandi 1991; Pai 1995; Quero 1997; Shi 1997; Xing 2003; Zeng 2003; Raza 2004; Riggio 2005; Mittal 2011; Sharma 2011; Agrawal 2012; Jain 2013; Ziada 2013), and 22 assessed the electroencephalogram mean cycle frequency (Elkington 1969; Brown 1971; Germain 1973; Rodgers 1973; Corazza 1982; Heredia 1987; Morgan 1987a; Morgan 1987b; Uribe 1987a; Uribe 1987b; Heredia 1988; Morgan 1989; Riggio 1989; Pai 1995; Jankovic 1996; Horsmans 1997; Quero 1997; Xing 2003; Zeng 2003; Raza 2004; Riggio 2005; Agrawal 2012).

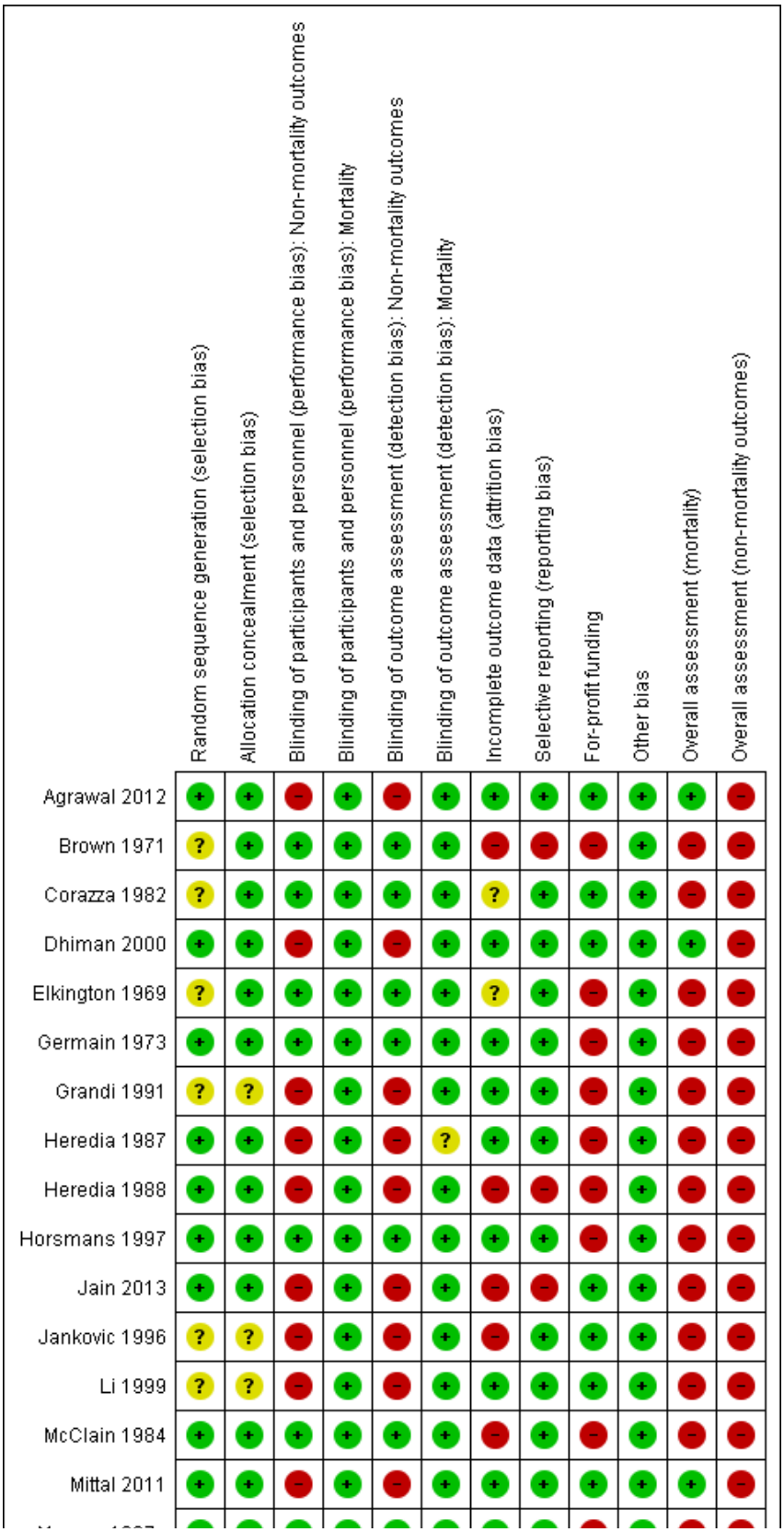
Excluded studies

We excluded four RCTs and 20 observational studies (Characteristics of excluded studies). Three RCTs compared lactulose versus probiotics (Sharma 2008), polyethylene glycol followed by lactulose (Rahimi 2014), or a carbon adsorbent (Pockros 2009), while one RCT compared mannitol lavage versus a combination of lactulose and the antibiotic kanamycin (Quinton 1982). Five case series described the effects of lactulose on minimal (Salerno 1994) or recurrent hepatic encephalopathy (Brown 1970; Rorsman 1970; Zeegen 1970; Bircher 1971). One additional study looked at the differential effects of lactitol and lactulose on chronic hepatic encephalopathy (Lanthier 1985), while another looked at the effect of lactulose in preventing hepatic encephalopathy following insertion of a transjugular intrahepatic portosystemic shunt (Piotraschke 1996). Three studies of participants with cirrhosis described compliance with non-absorbable disaccharides, the predictors of recurrence of hepatic encephalopathy, and the predictors of response (Bajaj 2010b; Sharma 2009a; Sharma 2010). Three studies describe the prevalence and characteristics of participants with overt or minimal hepatic encephalopathy (Schomerus 1993; Sharma 2010a), or young people admitted with overt hepatic encephalopathy (Sharma 2011a). Six studies describe the effects of non-absorbable disaccharides on cerebral blood flow and metabolism (James 1971), fat excretion (Merli 1992), terminal ileal and colonic pH (Patil 1987), blood ammonia, atrial natriuretic peptide and amino acid concentrations (Trovato 1995), blood ammonia, Number Connection Test results and lymphocyte subpopulations (Vendemiale 1992), and benzodiazepine-like compounds (Venturini 2005).

Risk of bias in included studies

We based our bias assessment on the published descriptions combined with additional information from investigators (Figure 2).

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



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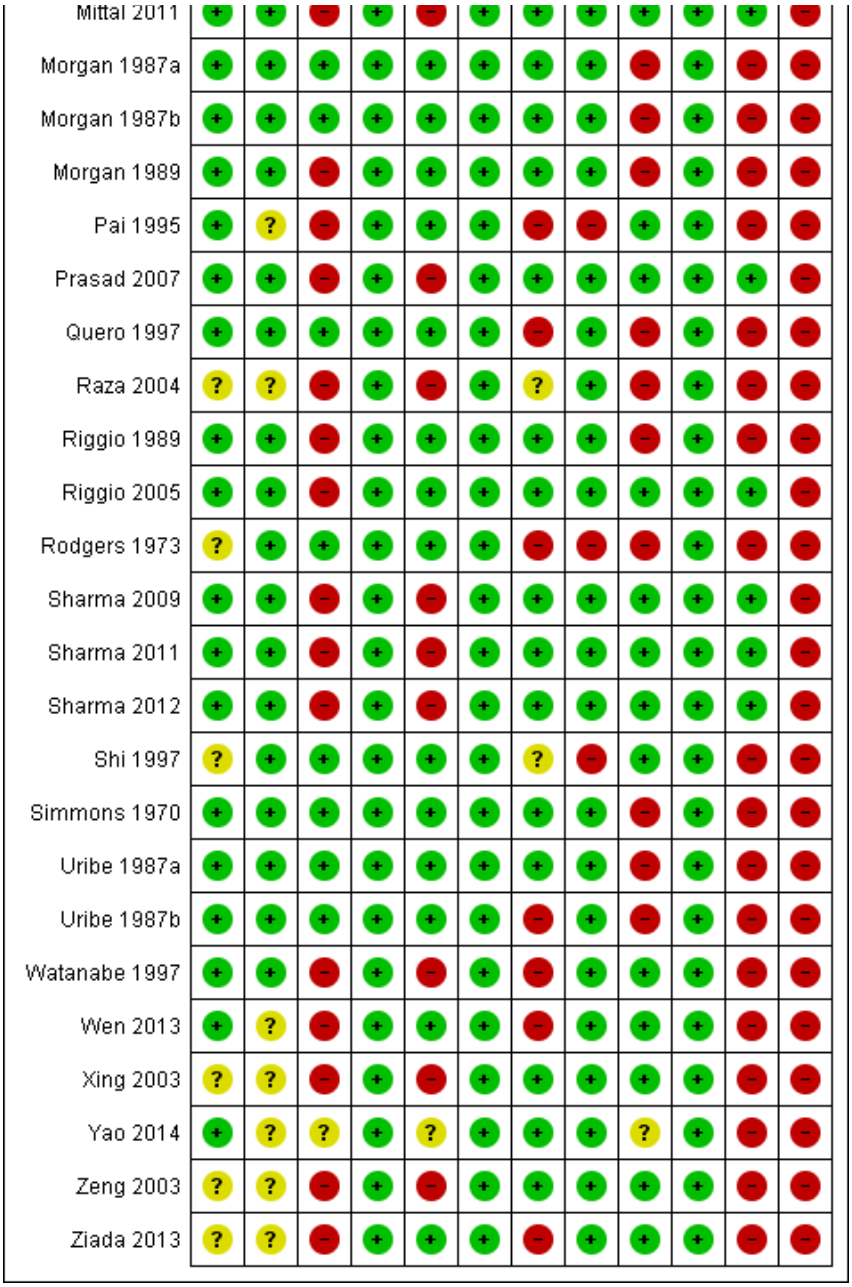


Allocation

In 26 RCTs, investigators generated the allocation sequence based on a table of random numbers or computer-generated random numbers (Simmons 1970; Germain 1973; McClain 1984; Heredia 1987; Morgan 1987a; Morgan 1987b; Uribe 1987a; Uribe 1987b; Heredia 1988; Morgan 1989; Riggio 1989; Pai 1995; Horsmans 1997; Quero 1997; Watanabe 1997; Dhiman 2000; Riggio 2005; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013; Wen 2013; Yao 2014).

In 28 RCTs, the allocation concealment involved randomisation via a central independent unit, serially numbered, opaque, sealed envelopes, or blinded administration of identically appearing drug containers (Elkington 1969; Simmons 1970; Brown 1971; Germain 1973; Rodgers 1973; Corazza 1982; McClain 1984; Heredia 1987; Morgan 1987a; Morgan 1987b; Uribe 1987a; Uribe 1987b; Heredia 1988; Morgan 1989; Riggio 1989; Horsmans 1997; Quero 1997; Shi 1997; Watanabe 1997; Dhiman 2000; Riggio 2005; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013).

We classified 23 RCTs as having low risk of selection bias (Simmons 1970; Germain 1973; McClain 1984; Heredia 1987; Morgan 1987a; Morgan 1987b; Uribe 1987a; Uribe 1987b; Heredia 1988; Morgan 1989; Riggio 1989; Horsmans 1997; Quero 1997; Watanabe 1997; Dhiman 2000; Riggio 2005; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013).

We classified 15 RCTs as having unclear risk of selection bias (Elkington 1969; Brown 1971; Rodgers 1973; Corazza 1982; Grandi 1991; Pai 1995; Jankovic 1996; Shi 1997; Li 1999; Xing 2003; Zeng 2003; Raza 2004; Wen 2013; Ziada 2013; Yao 2014).

Blinding

We classified five single-blind RCTs with blinded outcome assessment as having low risk of detection bias (Morgan 1989; Riggio 1989; Pai 1995; Riggio 2005; Wen 2013), and 14 double-blind RCTs as having low risk of performance and detection bias (Elkington 1969; Simmons 1970; Brown 1971; Germain 1973; Rodgers 1973; Corazza 1982; McClain 1984; Morgan 1987a; Morgan 1987b; Uribe 1987a; Uribe 1987b; Horsmans 1997; Quero 1997; Shi 1997).

The remaining 19 RCTs were open and we classified them as having high risk of performance and detection bias (Heredia 1987; Heredia 1988; Grandi 1991; Jankovic 1996; Watanabe 1997; Li 1999; Dhiman 2000; Xing 2003; Zeng 2003; Raza 2004; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013; Ziada 2013; Yao 2014).

Incomplete outcome data

In 12 trials, the authors described missing outcome data and excluded participants who were dropouts or withdrawals from their analyses (Brown 1971; Rodgers 1973; McClain 1984; Uribe 1987b; Heredia 1988; Pai 1995; Jankovic 1996; Quero 1997; Watanabe 1997; Jain 2013; Wen 2013; Ziada 2013). We classified these RCTs as having high risk of attrition bias and four RCTs as having unclear risk of attrition bias because the trial reports did not describe dropouts or withdrawals or the handling of missing outcome data in the analyses (Elkington 1969; Corazza 1982; Shi 1997; Raza 2004).

The remaining 22 RCTs had no missing outcome data and the analyses included all participants based on the intention-to-treat principle using adequate methods including last observation carried forward or multiple imputation (Simmons 1970; Germain 1973; Heredia 1987; Morgan 1987a; Morgan 1987b; Uribe 1987a; Morgan 1989; Riggio 1989; Grandi 1991; Horsmans 1997; Li 1999; Dhiman 2000; Xing 2003; Zeng 2003; Riggio 2005; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Yao 2014). We classified these RCTs as having low risk of attrition bias.

Selective reporting

Thirty-two RCTs reported predefined, clinically relevant outcome measures suggesting a low risk of selective reporting (Elkington 1969; Simmons 1970; Germain 1973; Corazza 1982; McClain 1984; Morgan 1987a; Morgan 1987b; Uribe 1987a; Uribe 1987b; Heredia 1988; Morgan 1989; Riggio 1989; Grandi 1991; Pai 1995; Jankovic 1996; Horsmans 1997; Quero 1997; Watanabe 1997; Li 1999; Dhiman 2000; Xing 2003; Zeng 2003; Raza 2004; Riggio 2005; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Wen 2013; Yao 2014).

One trial reported different primary and secondary outcomes in the electronic trial register (Jain 2013). The remaining five RCTs did not report mortality (Brown 1971; Rodgers 1973; Heredia 1988; Shi 1997; Ziada 2013). We therefore classed these six RCTs as having a high risk of selective reporting.

For-profit funding

Twenty RCTs did not receive funding or had other involvement with for-profit companies (Corazza 1982; Heredia 1987; Pai 1995; Jankovic 1996; Shi 1997; Watanabe 1997; Li 1999; Dhiman 2000; Xing 2003; Zeng 2003; Riggio 2005; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013; Wen 2013; Ziada 2013).

In 10 RCTs, investigators received lactitol, lactulose, or placebo from a pharmaceutical company (Simmons 1970; McClain 1984; Morgan 1987a; Morgan 1987b; Heredia 1988; Morgan 1989; Riggio 1989; Grandi 1991; Horsmans 1997; Raza 2004).

Seven RCTs received financial or other support from a pharmaceutical company (Brown 1971; Elkington 1969; Germain 1973; Quero 1997; Rodgers 1973; Uribe 1987a; Uribe 1987b).

One RCT did not report funding (Yao 2014).

Other potential sources of bias

We found no other potential sources of bias and therefore classified all RCTs as having low risk of bias for this domain (Elkington 1969; Simmons 1970; Brown 1971; Germain 1973; Rodgers 1973; Corazza 1982; McClain 1984; Heredia 1987; Morgan 1987a; Morgan 1987b; Uribe 1987a; Uribe 1987b; Heredia 1988; Morgan 1989; Riggio 1989; Grandi 1991; Pai 1995; Jankovic 1996; Horsmans 1997; Quero 1997; Shi 1997; Watanabe 1997; Li 1999; Dhiman 2000; Xing 2003; Zeng 2003; Raza 2004; Riggio 2005; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013; Wen 2013; Ziada 2013; Yao 2014).

Overall bias assessment

We classified eight RCTs as having low risk of bias in the assessment of mortality (Dhiman 2000; Riggio 2005; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012), and none of the RCTs as having low risk of bias in the assessment of the remaining outcomes.

Effects of interventions

See: **Summary of findings for the main comparison** Non-absorbable disaccharides versus placebo/no intervention for the prevention and treatment of hepatic encephalopathy in people with cirrhosis; **Summary of findings 2** Lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis

Non-absorbable disaccharides versus placebo/no intervention

Primary outcomes

Our meta-analysis of mortality included 24 RCTs with 1487 participants (Analysis 1.1). Compared with placebo/no intervention, non-absorbable disaccharides were associated with a beneficial effect on mortality when including all randomised clinical trials (risk ratio (RR) 0.59, 95% confidence interval (CI) 0.40 to 0.87; I^2 = 0%) or the eight RCTs with a low risk of bias (RR 0.63, 95% CI 0.41 to 0.97; number needed to treat to benefit (NNTB) 19; Analysis 1.2).

Our meta-analysis of hepatic encephalopathy included 22 RCTs with 1415 participants (Analysis 1.3) and showed that compared with placebo/no intervention, non-absorbable disaccharides were

associated with a beneficial effect on hepatic encephalopathy (RR 0.58, 95% CI 0.48 to 0.69; I^2 = 43%; NNTB six participants). Twenty-four RCTs with 1487 participants reported serious adverse events (Analysis 1.4) that reflected liver-related morbidity such as liver failure, hepatorenal syndrome, and variceal bleeding (Table 2). Non-absorbable disaccharides had a beneficial effect on serious adverse events (RR 0.47, 95% CI 0.36 to 0.60; I^2 = 0%; Analysis 1.4). None of the RCTs evaluating hepatic encephalopathy or serious adverse events had a low risk of bias.

We conducted the Trial Sequential Analyses of primary outcomes with the relative risk reduction (RRR) downgraded to 30%. In the analysis of mortality, we set the CGR to 15%. When including all 24 RCTs (Figure 3), the cumulative Z-curve crossed the monitoring boundary after 1037 participants before reaching the heterogeneity adjusted information size. The cumulative Z-curve did not cross the monitoring boundary when we reduced the RRR to 20% and increased the diversity to 20%, or when we only included RCTs with a low risk of bias (Figure 4). When we conducted the Trial Sequential Analysis for the outcome hepatic encephalopathy, we initially set the CGR to 45% (Figure 5). The analysis found that the Z-curve crossed the monitoring boundary before reaching the information size of 581 participants and the analysis was confirmed when we decreased the RRR to 20% (information size 1337 participants) and increased diversity from 30% (model based) to 50% (information size 814 participants). Likewise, when analysing serious adverse events with the CGR set to 30%, the Z-curve crossed the monitoring boundary before reaching the required information size (737 participants; Figure 6). We confirmed the result in an analysis with RRR of 20% and diversity 20% (information size 1719 participants).

Figure 3. Trial Sequential Analysis of mortality in 24 RCTs evaluating non-absorbable disaccharides versus placebo/no intervention. The primary meta-analysis found a RR of 0.59 (95% CI 0.40 to 0.87). When we set the RRR to 30% and CGR to 15%, (power 80%, alpha 5%, and diversity 0%), the cumulative Z-curve (the green line) crossed the monitoring boundary (inward sloping line) after 1037 participants before reaching the heterogeneity adjusted information size. The cumulative Z-curve did not cross the monitoring boundary when we increased the diversity to 20% and reduced the RRR to 20%.

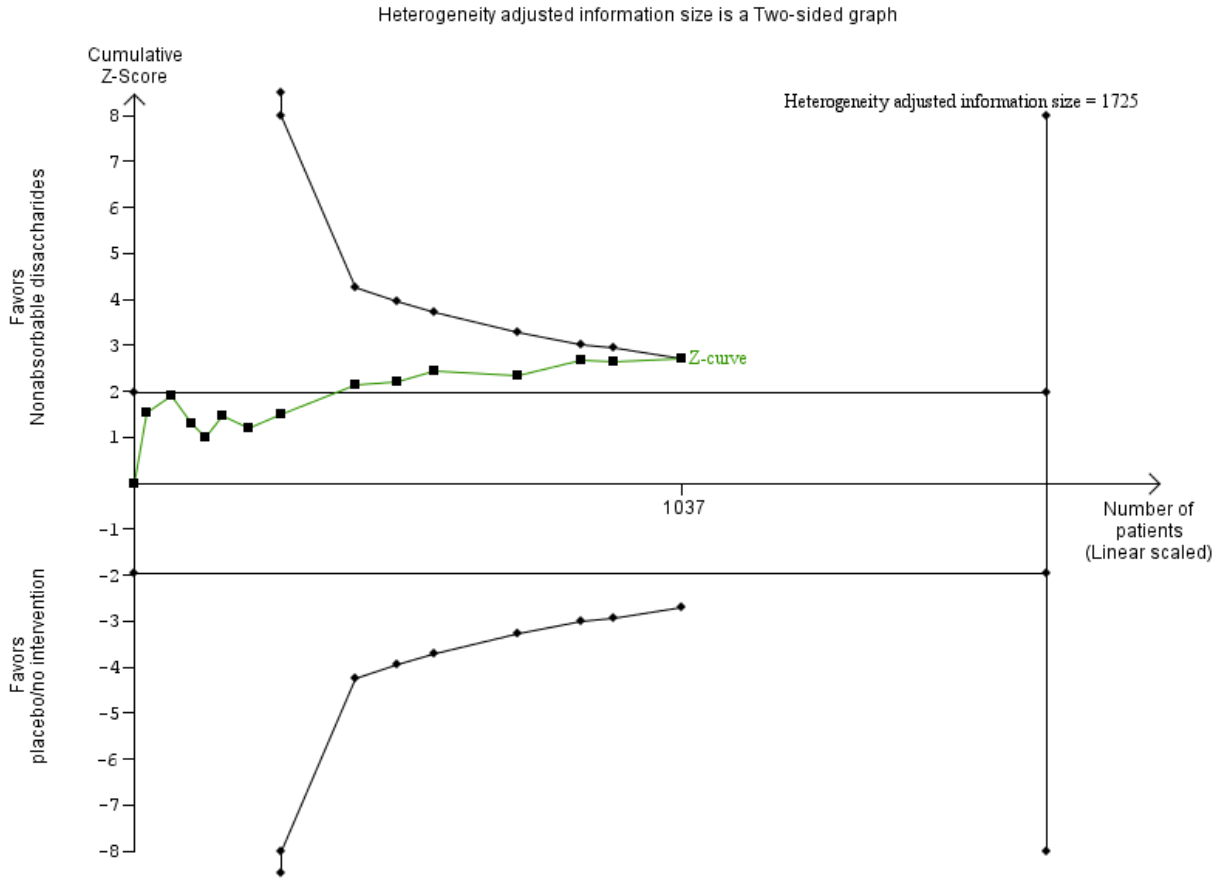


Figure 4. Trial Sequential Analysis of mortality in 8 RCTs with a low risk of bias. The RCTs compare non-absorbable disaccharides versus placebo/no intervention and the primary meta-analysis found an effect of non-absorbable disaccharides with a RR of 0.63 (95% CI 0.41 to 0.97). When we set the RRR to 30% and CGR to 45% (power 80%, alpha 5%, and diversity 0%), the cumulative Z-curve (the green line) did not cross the monitoring boundary (inward sloping line). The heterogeneity adjusted information size was 1725 participants.

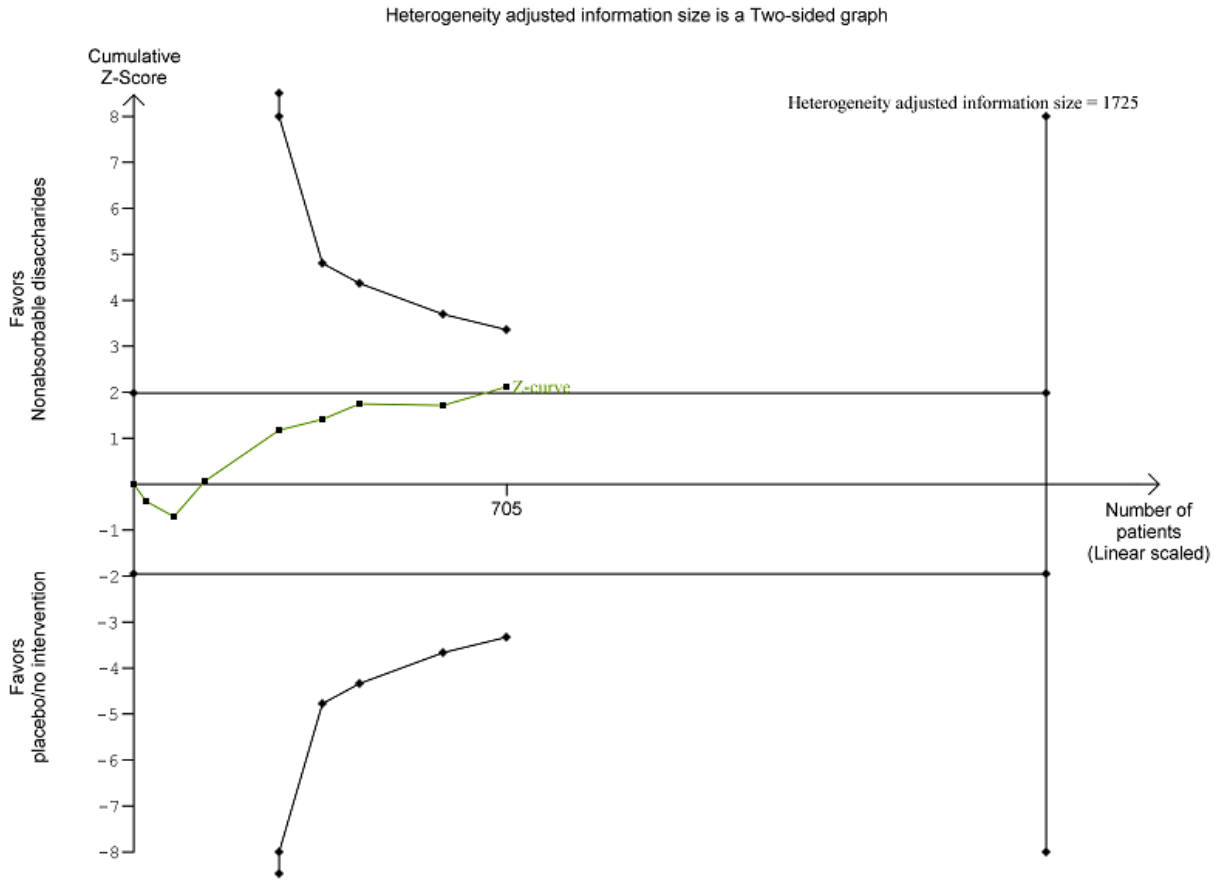


Figure 5. Trial Sequential Analysis of hepatic encephalopathy in 22 RCTs evaluating non-absorbable disaccharides versus placebo/no intervention. A meta-analysis including all trials found a RR of 0.58 (95% CI 0.48 to 0.69). The analysis includes a RRR of 30% and CGR of 45% (power 80%, alpha 5%, and diversity 30%). The analysis found that the Z-curve (green line) crossed the monitoring boundary (inward sloping black line) before reaching the information size of 581 participants. None of the RCTs were low risk of bias in the overall assessment. The Z-curve crossed the monitoring boundary before reaching the information size when we decreased the RRR to 20% (information size 1337 participants) and when we increased diversity to 50% (814 participants).

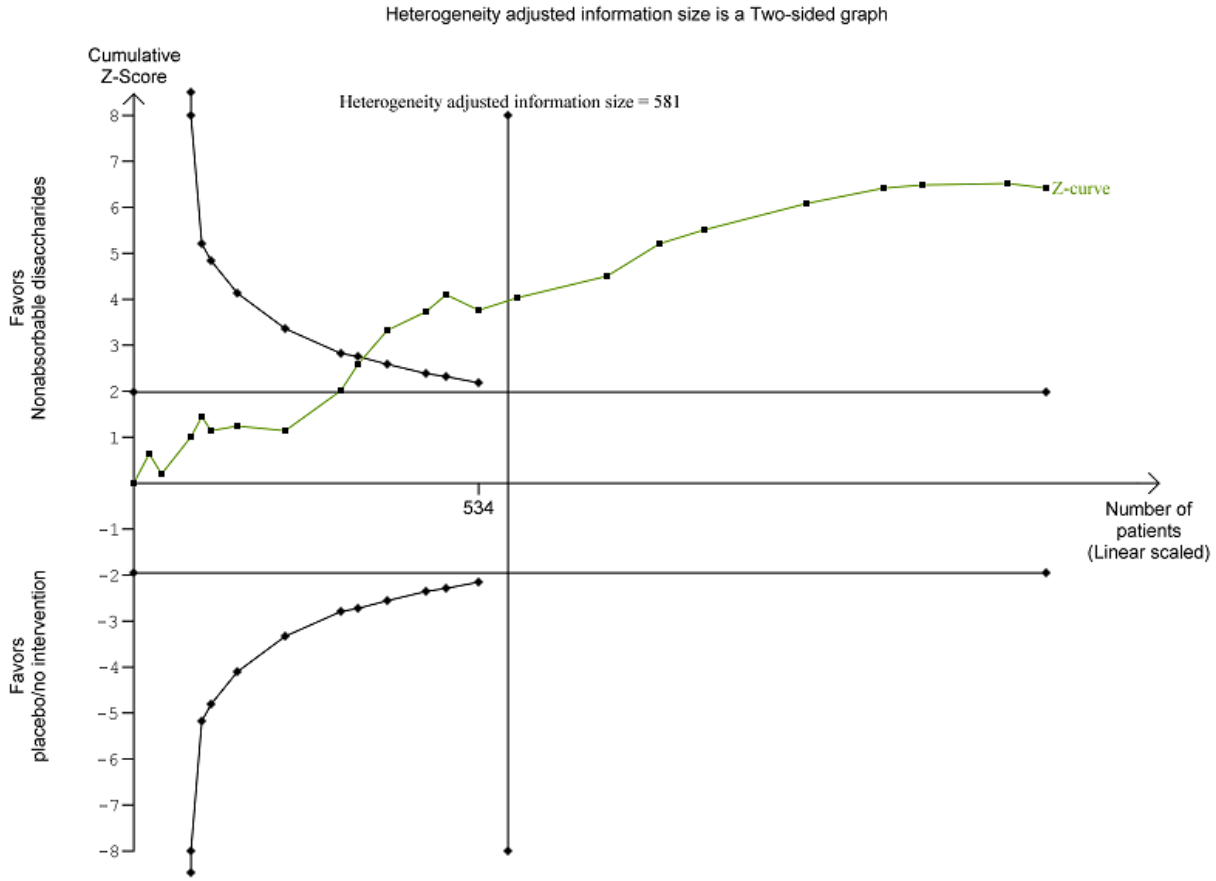
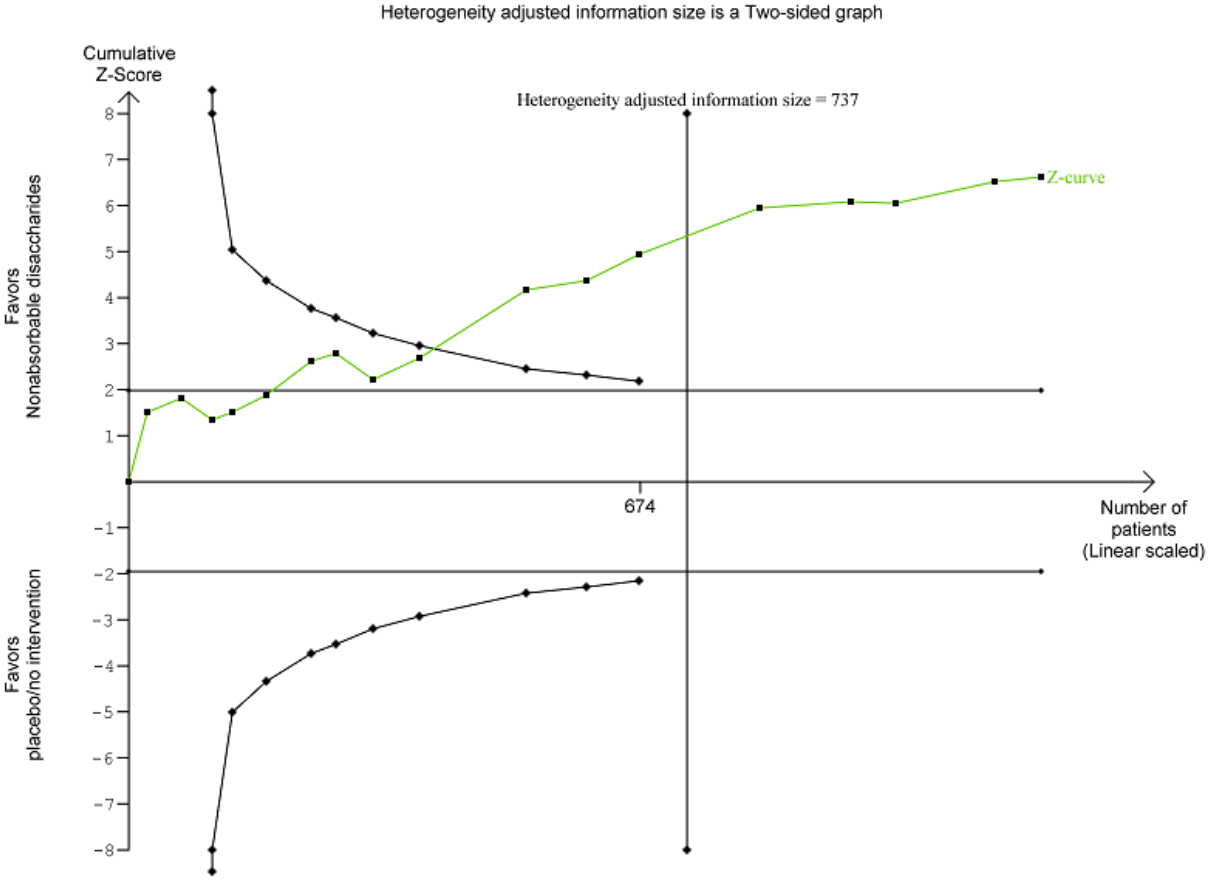


Figure 6. Trial Sequential Analysis of serious adverse events including 24 RCTs evaluating non-absorbable disaccharides versus placebo/no intervention. The primary meta-analysis found a beneficial intervention effect with a RR of 0.47 (95% CI 0.36 to 0.60). None of the included RCTs had a low risk of bias in the overall assessment. When conducting the Trial Sequential Analysis with RRR 30%, CGR 30%, power 80%, alpha 5%, and diversity 0%, the Z-curve crossed the monitoring boundary before reaching the required information size of 737 participants. The Z-curve also crossed the monitoring boundary before reaching the required information size when we reduced the RRR to 20% (information size 1719 participants) and when we increased diversity to 20% (information size 921 participants).



Worst-case scenario analyses (missing outcome data counted as failures) showed that the non-absorbable disaccharides were associated with a beneficial effect on mortality (RR 0.61, 95% CI 0.42 to 0.88; Analysis 1.10), hepatic encephalopathy (RR 0.59, 95% CI 0.50 to 0.69; Analysis 1.11), and serious adverse events (RR 0.47, 95% CI 0.37 to 0.61; Analysis 1.12). The 'extreme worst-case scenario' analyses (missing outcome data counted as failures in the non-absorbable disaccharide group and successes in the control group) reached the same conclusions (Analysis 1.10, Analysis 1.11, and Analysis 1.12).

Regression analyses and funnel plots showed no evidence of small study effects in the analysis of mortality (P value = 0.73), hepatic encephalopathy (P value = 0.93), or serious adverse events (P value = 0.96).

Secondary outcomes

Six RCTs included quality of life assessments (McClain 1984; Quero 1997; Watanabe 1997; Zeng 2003; Prasad 2007; Mittal 2011).

Three RCTs, Quero 1997, Prasad 2007 and Mittal 2011, evaluated 160 participants with minimal hepatic encephalopathy using the Sickness Impact Profile (Table 3; Table 4; Table 5), which includes 136 questions about health-related dysfunction (Gilson 1975; SF 36 questionnaire). The responses to these questions are divided into 12 categories: ambulation, body care/movement, mobility, emotional behaviour, social interaction, alertness behaviour, communication, work, sleep and rest, eating, home management, and recreation/pastimes. These, in turn, are used to inform the two major summative domains physical and psychosocial health. Two RCTs defined the alteration in the total score after treatment as the change in the overall quality of life (Prasad 2007; Mittal 2011). The third trial compared the end of treatment values (Quero 1997). The three RCTs individually found a beneficial effect of lactulose. However, the heterogeneity between RCTs was considerable so we did not conduct a meta-analysis (Analysis 1.5).

One trial, Zeng 2003, used an abbreviated version of the World Health Organization quality of life 100 questionnaire (WHOQOL

1998), which evaluates the domains: physical health, psychological health, social relationships, and environment. The trial report includes a table showing a selection of subscores from the questionnaire (Table 6). The analyses showed that lactulose improved the domains of physical and psychological health, and social relationships (P value < 0.05 for all subscores).

One trial described the effect of lactulose on the quality of life without specifying the assessment method (Watanabe 1997). The abstract states that lactulose improved the quality of life without providing quantitative data. One further trial, McClain 1984, assessed quality of life using the Katz functioning scale (Katz 1963), which evaluates the adjustment and social behaviour in the community. The investigators state that there were no differences between the intervention groups before or after treatment, but do not provide quantitative data.

The non-absorbable disaccharides increased the risk of gastrointestinal non-serious adverse events (RR 2.47, 95% CI 1.24 to 4.93; 739 participants; nine RCTs; I^2 = 64%; Analysis 1.6), including diarrhoea, bloating, flatulence, and nausea. Participants allocated to placebo/no intervention had a higher risk of constipation.

The surrogate outcomes included Number Connection Test results (mean difference (MD) -5.56, 95% CI -11.59 to 0.47; Analysis 1.7) and blood ammonia concentrations assessed at the end of the trials (MD -11.64, 95% CI -21.14 to -2.14; Analysis 1.8) and as the change from baseline to the end of follow-up (MD 18.97, 95% CI 8.86 to 29.09; Analysis 1.9). The analyses included a small number of participants and considerable heterogeneity.

Prevention RCTs

The meta-analysis evaluating primary or secondary prevention showed a beneficial effect on mortality when including all six RCTs (RR 0.63, 95% CI 0.40 to 0.98; 668 participants; Analysis 2.1), or the five RCTs with a low risk of bias (RR 0.64, 95% CI 0.41 to 0.99; 538 participants; Analysis 2.2). The non-absorbable disaccharides also had beneficial effects on the prevention of hepatic encephalopathy (RR 0.47, 95% CI 0.33 to 0.68; Analysis 2.3), and serious adverse events (RR 0.48, 95% CI 0.33 to 0.70, Analysis 2.4). Additional analyses including four RCTs showed that non-absorbable disaccharides increased the risk of non-serious adverse events (RR 2.78, 95% CI 1.50 to 5.13; 548 participants; Analysis 2.5).

Treatment RCTs

The meta-analysis evaluating the treatment of overt or minimal hepatic encephalopathy showed no effect of non-absorbable disaccharides on mortality when including all 18 RCTs (RR 0.49, 95% CI 0.23 to 1.05; 819 participants; Analysis 3.1), or the three RCTs with a low risk of bias (RR 0.56, 95% CI 0.12 to 2.68; 167 participants; three RCTs; Analysis 3.2). The analyses showed beneficial effect of non-absorbable disaccharides on mortality in RCTs evaluating acute, overt hepatic encephalopathy (RR 0.36, 95% CI 0.14 to 0.94; 172 participants; six RCTs), but not in RCTs evaluating minimal hepatic encephalopathy (RR 0.82, 95% CI 0.24 to 2.86; 647 participants; 12 RCTs). No events occurred in RCTs evaluating chronic hepatic encephalopathy (Analysis 3.3).

The non-absorbable disaccharides had beneficial effects on overt and minimal hepatic encephalopathy (RR 0.63, 95% CI 0.53 to 0.74; 747 participants; 16 RCTs; Analysis 3.4). The effect was similar in RCTs evaluating acute or chronic hepatic encephalopathy (Analysis 3.5). Non-absorbable disaccharides had a beneficial effect on serious adverse events (RR 0.42, 95% CI 0.26 to 0.69; 819 participants; 18 RCTs; Analysis 3.6) with no difference between the acute and chronic hepatic encephalopathy subgroups (Analysis 3.7). Non-absorbable disaccharides did not increase the risk of non-serious adverse events (RR 2.12, 95% CI 0.62 to 7.28; 191 participants; five RCTs; Analysis 3.7).

Lactulose versus lactitol

Meta-analyses showed no difference between lactulose versus lactitol in the assessment of mortality (RR 1.30, 95% CI 0.59 to 2.85; 225 participants; eight RCTs; I^2 = 0%; Analysis 4.1), hepatic encephalopathy (RR 1.00, 95% CI 0.84 to 1.19; Analysis 4.2), or serious adverse events (RR 1.56, 95% CI 0.84 to 2.88; Analysis 4.3). All Trial Sequential Analyses ignored the monitoring boundaries because the information size was insufficient. None of the RCTs assessed the quality of life. The non-serious adverse events were mainly gastrointestinal (RR 1.55, 95% CI 0.88 to 2.74; Analysis 4.4). We found no differences between interventions for the surrogate outcomes Number Connection Test (end of treatment Analysis 4.5 or change from baseline Analysis 4.6), or blood ammonia concentrations (end of treatment Analysis 4.7 or change from baseline Analysis 4.8). We found no differences between subgroups for any outcomes. We only found evidence of missing outcome data in two RCTs (Pai 1995; Jankovic 1996). The trials did not provide information about the number of participants in the two groups (lactulose or lactitol) with missing outcome data. Therefore, we were unable to conduct worst-case scenario or extreme worst-case scenario analyses.

'Summary of findings' tables

In the analyses comparing non-absorbable disaccharides versus placebo/no intervention (Summary of findings table 1), we downgraded the quality of the evidence to '*moderate*' for the outcome mortality because the Trial Sequential Analysis of RCTs with a low risk of bias found no evidence to support or refute an intervention effect. Likewise, we downgraded the quality of evidence for the outcomes hepatic encephalopathy and serious adverse events one level to '*moderate*' because none of the included RCTs had a low risk of bias. We downgraded the outcome quality of life three levels to '*very low quality evidence*' because none of the included RCTs had a low risk of bias, the heterogeneity was considerable, and we were unable to combine the data in an overall analysis. We also downgraded the outcome non-serious adverse events three levels to '*very low quality evidence*' because none of the included RCTs had a low risk of bias, the confidence intervals were wide, and we were only able to include data from nine RCTs in our meta-analysis.

In the analyses comparing lactulose versus lactitol (Summary of findings table 2), we downgraded the evidence three levels to '*very low quality*' due to imprecision, uncertainty, and a methodological quality (none of the included RCTs had a low risk of bias).

DISCUSSION

Summary of main results

This review includes descriptive information from 38 randomised clinical trials (RCTs) with 1828 participants and quantitative data from 34 RCTs with 1764 participants. The primary analyses show that use of the non-absorbable disaccharides, lactulose

and lactitol, is associated with reduced mortality compared with placebo/no intervention when including all RCTs and when including the RCTs with a low risk of bias. In subgroup analyses, we found no statistical differences between RCTs stratified by the type of hepatic encephalopathy. We found a beneficial effect on mortality in RCTs evaluating prevention and RCTs evaluating acute hepatic encephalopathy, but not in RCTs evaluating chronic or minimal hepatic encephalopathy (where the mortality rates overall were extremely low). The quality of the evidence was moderate.

Use of non-absorbable disaccharides is associated with a beneficial effect on the prevention and treatment of hepatic encephalopathy (*moderate quality evidence*). Additional analyses showed that non-absorbable disaccharides can help to reduce serious adverse events associated with the underlying liver disease including liver failure, variceal bleeding, and hepatorenal syndrome (*moderate quality evidence*). Six RCTs suggested a beneficial effect on quality of life, but we were unable to combine the results in a meta-analysis (*very low quality evidence*). As expected, the non-absorbable disaccharides increased the risk of non-serious gastrointestinal adverse events (*very low quality evidence*). None of the RCTs comparing lactulose versus lactitol assessed quality of life. Analyses of the remaining outcomes found no differences between the two interventions (*very low quality evidence*).

Overall completeness and applicability of evidence

The most important outcomes for people with cirrhosis and hepatic encephalopathy are mortality, morbidity, adverse events, and quality of life (Bajaj 2011a). We included information on all of these outcomes. The RCTs evaluated improvement in hepatic encephalopathy using a variety of methods. This partly reflects that fact that the included RCTs were conducted between 1969 and 2014 during which time diagnostic criteria changed on more than one occasion. The included RCTs often used clinical or composite scoring systems and a categorical approach to define improvement (or lack thereof). The investigators did not use the same thresholds to define improvement, so we chose to use the definitions that they defined as clinically relevant. The diagnostic classification of hepatic encephalopathy also changed during the time period (EASL and AASLD guideline 2014a; EASL and AASLD guideline 2014b). Thus, we made a decision *a priori* to utilise the individual primary investigators' classification of the type of hepatic encephalopathy and the outcome criteria for hepatic encephalopathy, based on the argument that these decisions will have been made using the criteria that were most clinically relevant when the investigators conducted the trial.

The older RCTs often used co–interventions such as dietary protein restriction. Although the RCTs did not use the co-interventions consistently, participants randomised to experimental or control groups within a given RCT would have had equal access to them. This might result in heterogeneity, but not in systematic differences between groups.

Hepatic encephalopathy varies widely in its manifestations. The RCTs included in our review represent the entire spectrum of the syndrome encountered in people with cirrhosis. Thus, RCTs included people experiencing an acute episode of hepatic encephalopathy, chronic hepatic encephalopathy associated with advanced liver disease, spontaneous or surgically created portal-systemic shunts, and minimal hepatic encephalopathy. In addition, the included RCTs explored the use of non-absorbable disaccharides for primary and secondary prevention of hepatic encephalopathy. The fact that the RCTs address all the objectives of the review strengthens the completeness of the evidence. We included all RCTs with extractable data in our primary analyses. We also conducted subgroup, sensitivity, and regression analyses to determine the differential effects of intervention on the clinical variants. Our analyses showed that non-absorbable disaccharides are associated with stable beneficial effects on clinically important outcomes across the different groups. This supports the external validity of our findings.

This review includes the two commercially available disaccharides, lactulose and lactitol. However, only four of the 28 RCTs of non-absorbable disaccharides versus placebo/no treatment utilised lactitol (Uribe 1987a; Uribe 1987b; Shi 1997; Riggio 2005). Nine RCTs with a total of 248 participants compared lactulose versus lactitol (Heredia 1987; Morgan 1987a; Morgan 1987b; Heredia 1988; Morgan 1989; Riggio 1989; Grandi 1991; Pai 1995; Jankovic 1996). We found no differences between the two interventions, but the statistical power was insufficient.

People with non-cirrhotic portal hypertension and those with fulminant hepatic failure may also develop hepatic encephalopathy. They are encountered much less frequently in clinical practice and were not represented in the included trials. There is no reason to suppose that our results cannot be extrapolated to people with hepatic encephalopathy associated with non-cirrhotic portal hypertension, e.g. portal vein block. However, the situation in people with fulminant hepatic failure is much more complex and the result may not be directly applicable.

Episodes of hepatic encephalopathy often develop in response to a precipitating event such as infection, gastrointestinal bleeding, alcohol misuse, or electrolyte disturbances. Identification and treatment of these precipitating factors is key to the management of affected individuals although no obvious precipitating factor is identified in 50% of instances (EASL and AASLD guideline 2014a; EASL and AASLD guideline 2014b). Avoiding likely precipitants such as constipation, dietary indiscretion, and certain medications can also reduce the risk of developing hepatic encephalopathy in the longer term. It is not clear whether use of non-absorbable disaccharides provides additional benefit in situations where hepatic encephalopathy is precipitated by a treatable event. The RCTs included in our review do not provide detailed information on possible precipitating events, on the effects of interventions designed to ameliorate them, or on the effects, if any, of the addition of a non-absorbable disaccharide. However, in two of the included RCTs, non-absorbable disaccharides, used together with measures to manage upper gastrointestinal haemorrhage, prevented the development of hepatic encephalopathy (Sharma 2012; Wen 2013).

Non-adherence to non-absorbable disaccharides is generally ascribed to adverse gastrointestinal effects such as unpredictable diarrhoea, bloating, flatulence, and abdominal pain (Bajaj 2010c; Volk 2012). Although we did find that treatment with lactulose or lactitol was associated with a higher risk of these non-serious adverse events, none of the RCTs included in our review evaluated compliance in a manner that allowed us to assess the potential influence of these gastrointestinal effects. Other factors may, however, be important in determining compliance with treatment both on the part of the person receiving treatment and the physician prescribing it. Thus, people with hepatic encephalopathy

may be unaware of the need for long-term treatment, may be unable to effectively titrate the dosage, and may find the side effects inconvenient especially when away from home. The physician may fail to explain the multiple ways in which non-absorbable disaccharides produce their beneficial effects and by placing undue focus on the need for them to pass two semi-soft stools/day may foster the belief that as long as this is achieved, there is no real need to take the medication. They may also erroneously assume that people will comply with treatment and hence fail to check adherence.

Hepatic encephalopathy imposes a significant burden on healthcare systems and the resource utilisation associated with the management of people with hepatic encephalopathy is increasing (Poordad 2007). The increased costs do not seem to reflect the duration of hospitalisation, which has decreased, but a combination of direct and indirect factors such as the costs of treatment and rehabilitation after hospitalisation (Neff 2010). None of the RCTs included in the present review assessed the costs associated with hospitalisation, but we found a clear beneficial effect of non-absorbable disaccharides in preventing the development and recurrence of hepatic encephalopathy that would generally require hospitalisation. Use of non-absorbable disaccharides is also associated with a reduction in the occurrence of serious liver-related complications. This will also result in reduced hospitalisations and lengths of hospital stay.

Quality of the evidence

The previous version of this review identified several potential biases in included RCTs (Als-Nielsen 2004). In this updated review, we identified a larger number of RCTs and additional information on essential aspects of bias control. As recommended, we combined the individual bias domains in an overall assessment (Gluud 2015). We also included an assessment of individual domains, focusing on RCTs with a low risk of selection bias (Higgins 2011a; Higgins 2011b; Savovic 2012). Based on previous evidence (Savovic 2012), we defined mortality, but not serious adverse events, as an outcome that is robust to performance and detection bias. This decision can be questioned as lack of blinding is not likely to influence the assessment of events such as variceal bleeding, hepatorenal syndrome, and liver failure. We included 14 double-blind RCTs and cannot exclude the possibility that our analyses overestimate the effect of non-absorbable disaccharides on hepatic encephalopathy due to lack of blinding. In contrast to the previous version of this review, we included any type of for-profit funding as a bias domain (Gluud 2015). The decision to include this domain is debatable (Higgins 2011a; Higgins 2011b). The fact that we included gratuitous supply of interventions or placebo was the main reason why we did not identify RCTs comparing lactulose versus lactitol with a low risk of bias in the overall assessment. Based on the revised assessment of bias control combined with the assessment of the directness of evidence, heterogeneity, precision of effect estimate, and risk of publication bias we classified the quality of the evidence as *moderate* for the assessment of our primary outcomes mortality, hepatic encephalopathy, and serious adverse events.

The included RCTs were conducted world-wide. The country/continent of origin included India/Pakistan (Dhiman 2000; Raza 2004; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013), the USA (Elkington 1969; Simmons 1970; Brown 1971; Rodgers 1973; McClain 1984), the Far-East (Pai 1995; Shi 1997; Li 1999; Xing 2003; Zeng 2003; Wen 2013), Europe (Germain 1973; Corazza 1982; Heredia 1987; Morgan 1987a; Morgan 1987b; Heredia 1988; Morgan 1989; Riggio 1989; Grandi 1991; Jankovic 1996; Horsmans 1997; Quero 1997; Riggio 2005), Mexico (Uribe 1987a; Uribe 1987b), and Egypt (Ziada 2013). A single centre in India conducted eight of the RCTs (Dhiman 2000; Prasad 2007; Sharma 2009; Mittal 2011; Sharma 2011; Agrawal 2012; Sharma 2012; Jain 2013). Four of these RCTs involved participants with minimal hepatic encephalopathy (Dhiman 2000; Prasad 2007; Mittal 2011; Jain 2013), and four evaluated primary and secondary prophylaxis (Sharma 2009; Sharma 2011; Agrawal 2012; Sharma 2012). The results of the RCTs evaluating minimal hepatic encephalopathy did not differ substantially from those in the similar RCTs undertaken in centres outside of India. We found no comparable prevention studies undertaken outside of India. Two prevention RCTs conducted in Italy looked at the effects of non-absorbable disaccharides following transjugular intrahepatic portosystemic shunt insertion (Riggio 1989; Riggio 2005). The RCTs found no benefit on mortality, hepatic encephalopathy, or serious adverse events. However, this is a notoriously difficult situation to manage and one that depends more on careful pre-selection of candidates than on *post-hoc* exhibition of pharmacotherapy. One RCT conducted in China looked at the effect of lactulose in the prevention of hepatic encephalopathy following an acute upper gastrointestinal bleed and observed significant benefit (Wen 2013). We observed clinical variation in participant demographics between the prevention RCTs conducted in India and those conducted elsewhere, but variables such as age, gender, and the aetiology of the cirrhosis did not confound the results. RCTs evaluating the effects of non-absorbable disaccharides for primary and secondary prevention conducted in countries outside of India would strengthen the external validity of our findings.

Potential biases in the review process

A recent methodological review drew attention to outcome reporting bias in systematic reviews (Page 2014). Changes between the outcomes in protocols and published systematic reviews include the statistical significance of the results for those outcomes. We updated this review to incorporate current recommendations (Higgins 2011a; Higgins 2011b; Gluud 2015). The methods used in this update differ from those in the previous version (Als-Nielsen 2004a; Als-Nielsen 2004b; Als-Nielsen 2005). As part of the update, we changed the definition of our primary outcomes to provide information on benefits as well as harms. Accordingly, we now include serious adverse events as a primary rather than a secondary outcome measure.

The selective publication of RCTs with a positive result increases the risk of outcome reporting bias (Dwan 2008). The RCTs included in the present review were all published as full paper articles and this might be interpreted as a potential publication bias. However, we combined our electronic searches with extensive manual searches of reference lists and conference proceedings. We identified a large number of abstracts, but all were published subsequently as full papers. We found no evidence of publication bias or other small study effects and very few RCTs showed evidence of outcome reporting bias. Of the 29 RCTs on non-absorbable disaccharides versus placebo or no intervention, we were unable to include data for primary outcomes from four RCTs with 64 participants (Elkington 1969; Brown 1971; Rodgers 1973; Shi 1997). The RCTs are small and the narrative information in the published reports suggested that the intervention had a beneficial effect on hepatic

encephalopathy. Exclusion of these four RCTs is unlikely to change our conclusions.

Agreements and disagreements with other studies or reviews

The previous version of this review assessed the effect of non-absorbable disaccharides versus placebo/no intervention and lactulose versus lactitol based on a total of 19 RCTs (Als-Nielsen 2004). Eleven RCTs compared lactulose or lactitol versus placebo/no intervention (Elkington 1969; Simmons 1970; Germain 1973; Rodgers 1973; Corazza 1982; Uribe 1987a; Uribe 1987b; Shi 1997; Watanabe 1997; Li 1999; Dhiman 2000), and eight RCTs compared lactulose versus lactitol (Heredia 1987; Morgan 1987a; Morgan 1987b; Heredia 1988; Morgan 1989; Riggio 1989; Grandi 1991; Pai 1995). Based on a meta-analyses including four RCTs with 85 participants, the review found no effect of non-absorbable disaccharides on mortality compared with placebo/no intervention (Simmons 1970; Germain 1973; Uribe 1987a; Dhiman 2000). A meta-analysis including six RCTs with 207 participants showed a beneficial effect on hepatic encephalopathy (Simmons 1970; Germain 1973; Uribe 1987a; Watanabe 1997; Li 1999; Dhiman 2000), but the effect was not confirmed in an analysis that only included RCTs with a low risk of bias. We included 38 RCTs (1828 participants) in our qualitative evaluation and 34 RCTs in our qualitative analyses. Our analyses include several different groups of participants from several countries. In spite of the clinical differences, our analyses showed negligible or moderate statistical heterogeneity. Our findings disagree with previous evidence, mainly because previous reviews included fewer RCTs.

The joint guidelines from the European and American Associations for the Study of the Liver made four recommendations of relevance to this review (EASL and AASLD guideline 2014a; EASL and AASLD guideline 2014b). *First*, that lactulose should be the first-choice treatment for an acute episode of overt hepatic encephalopathy in people with cirrhosis. *Second*, that lactulose should be used for prevention of recurrent episodes of hepatic encephalopathy after the initial episode. *Third*, that minimal hepatic encephalopathy should not be treated routinely. *Fourth*, that primary prophylaxis for prevention of the development of hepatic encephalopathy is not required in people with cirrhosis except if they are known to be at high risk.

In agreement with the guideline recommendations, we found a beneficial effect of non-absorbable disaccharides on clinical outcomes in RCTs evaluating secondary prevention and treatment. The guidelines do not recommend routine treatment of minimal hepatic encephalopathy or primary prevention of hepatic encephalopathy. Our analyses provide a large body of evidence showing that people with minimal hepatic encephalopathy benefit from non-absorbable disaccharides in relation to cognitive functioning and probably quality of life, and some evidence that non-absorbable disaccharides may be considered in primary prevention.

AUTHORS' CONCLUSIONS

Implications for practice

This review includes randomised clinical trials (RCTs) evaluating the prevention and treatment of hepatic encephalopathy in people with cirrhosis. The analyses found that non-absorbable disaccharides are associated with beneficial effects on mortality and hepatic encephalopathy and that non-absorbable disaccharides can help to reduce serious adverse events associated with the underlying liver disease including liver failure, hepatorenal syndrome, and variceal bleeding. The quality of the evidence was moderate. The interventions may also have a beneficial effect on quality of life, but we were unable to combine the data in meta-analyses. The non-serious gastrointestinal adverse events are well known and include diarrhoea, bloating, and flatulence. The quality of the evidence was very low for the secondary outcomes (quality of life and non-serious adverse events). The mean treatment duration depended on the type of encephalopathy, with five days for acute, 74 days for chronic, 70 days for minimal, and 207 days for prevention of hepatic encephalopathy. None of the RCTs comparing lactulose versus lactitol evaluated quality of life. The review found no differences between lactulose and lactitol for the remaining outcomes. The quality of the evidence was very low.

Implications for research

We used the EPICOT format (Brown 2006) in the definition of implications for research:

Evidence (what is the current state of the evidence?): this review includes 38 RCTs and provides moderate quality evidence that non-absorbable disaccharides have a beneficial effect on clinical outcomes. Additional research may be needed to further evaluate the effect of the intervention in specific subgroups.

Participants (what is the population of interest?): the largest body of evidence evaluated prevention of hepatic encephalopathy and people with minimal hepatic encephalopathy. Only a relatively small proportion of participants had chronic hepatic encephalopathy or an acute episode of hepatic encephalopathy. Future research may address the effect of non-absorbable disaccharides in these groups.

Interventions (what are the interventions of interest?): the interventions assessed include lactulose and lactitol.

Comparisons (what are the comparisons of interest?): placebo-controlled RCTs as well as RCTs comparing lactulose versus lactitol seem relevant. Future RCTs should also evaluate the effect of co-interventions.

Outcomes (what are the outcomes of interest?): RCTs should include an assessment of mortality, hepatic encephalopathy, and adverse events. Additional evidence evaluating the effect on quality of life is also needed.

Time stamp (date of literature search): October 2015.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agrawal 2012

Methods	Open, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 158 participants (see notes) with cirrhosis and a history, but no current evidence, of overt hepatic encephalopathy. In total, 71% of participants in the lactulose group and 73% in the control group had minimal hepatic encephalopathy at inclusion. Age (mean ± SD) • Lactulose group 41 ± 10.7 years • Control group 46.0 ± 11.2 years Proportion of men • Lactulose group 85.0% • Control group 78.2% Aetiology of cirrhosis • Alcohol 40.0% • Hepatitis B 20.9% • Hepatitis C 15.3%
Interventions	Lactulose syrup versus no intervention for 12 months
Outcomes	**Neuropsychiatric assessment** • Mental status (West Haven Criteria) • Number Connection Tests A and B • Figure Connection Tests A and B • Block design test • Digit symbol test • Critical Flicker Frequency • Arterial blood ammonia
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, adverse events, and blood ammonia concentrations assessed after 12 months
Inclusion period	October 2008 to December 2009
Country of origin	India
Notes	• The trial includes 158 participants randomly allocated to lactulose or no intervention and a third intervention arm with 77 participants allocated to a probiotic. The probiotic group is not included in our analyses. • The diagnosis of minimal hepatic encephalopathy was based on the presence of at least 2 abnormal psychometric tests. • The primary outcome of the trial was the development of overt hepatic encephalopathy, graded using the West Haven Criteria, at 12 months. • Secondary prophylaxis was defined as the prevention of recurrence of hepatic encephalopathy during the follow-up period in participants who had recovered from a previous episode of overt hepatic encephalopathy.

Agrawal 2012 *(Continued)*

- The model of end stage liver disease (MELD) score (mean ± SD) at inclusion was 19.2 ± 5.5 in the lactulose group and 18.5 ± 4.2 in the control group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. No blinding of the outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised and report intention-to-treat analyses that included all participants. Missing outcome data are unlikely to affect the analyses or to be associated with the outcome.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	Low risk	Low risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Brown 1971

Methods	Double-blind, cross-over, single-centre inpatient/outpatient trial
Participants	The trial includes 20 participants with advanced cirrhosis stabilised in hospital on a low protein diet and then given increasing amounts of protein until they developed overt hepatic encephalopathy. They were then randomised to treatment with lactulose or placebo (sorbitol), which they received for prescribed, but not standardised periods of time in rotation

Brown 1971 *(Continued)*

	• Patient characteristics: not reported
Interventions	Lactulose syrup versus placebo (sorbitol) for a maximum of 30 months (see notes)
Outcomes	**Neuropsychiatric assessment** • Clinical status (no specific overall score) • Subjective improvement e.g. ability to return to work • Blood ammonia • Electroencephalogram • Number of hospitalisations
Outcomes included in meta-analyses	No outcomes included in meta-analyses (see notes)
Inclusion period	Not reported
Country of origin	USA
Notes	• The investigators initially evaluated participants in hospital, but continued follow-up on an outpatient basis. Based on the text, we estimated that the maximum treatment duration was 30 months. • The published report excludes 11 participants for the following reasons: i) follow-up too short (n = 2); ii) non-compliant with treatment (n = 3); iii) managed with protein restriction alone (n = 3); iv) died due to acute alcoholic hepatitis (n = 2) or lymphoma (n = 1). The authors report that 9 of the remaining participants responded well with a reduction in the number of hospitalisations during treatment with lactulose. Illustrative narrative data are provided on 5 of these 9 participants. • We were unable to extract qualitative outcome data. • The investigators did not assess the quality of life directly, but indirectly via the subjective overall assessment of improvement (e.g. return to work).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Blinded administration of interventions
Blinding of participants and personnel (performance bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of participants and personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome

Brown 1971 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	The investigators do not account for all participants randomised (see notes).
Selective reporting (reporting bias)	High risk	Mortality data incomplete
For-profit funding	High risk	The trial received support in the form of a grant from a pharmaceutical company.
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Corazza 1982

Methods	Double-blind, parallel-arm, single-centre inpatient trial
Participants	The trial includes 32 participants with cirrhosis and chronic hepatic encephalopathy Age (mean ± SD) • Lactulose group 53.7 ± 2.6 years • Control group 54.1 ± 2.9 years Proportion of men • Lactulose group 37.5% • Control group 50.0% Aetiology of cirrhosis • Alcohol 87.5% • Hepatitis B 12.5%
Interventions	Lactulose syrup versus placebo for 10 days
Outcomes	**Neuropsychiatric assessment** • Mental status (Encephalopathy Intensity Score) • Blood ammonia • Electroencephalogram
Outcomes included in meta-analyses	Mortality, adverse events, and blood ammonia concentrations assessed after 10 days
Inclusion period	Not reported
Country of origin	Italy
Notes	• The trial includes 32 participants allocated to lactulose or placebo and a third allocation arm with 20 participants allocated to pyridoxine-alpha-ketoglutarate. The pyridoxine-alpha-ketoglutarate group is not included in our analyses.

Corazza 1982 *(Continued)*

- The trial describes the effects of the interventions on hepatic encephalopathy based on an overall score, but does not provide an assessment of the changes in the score from basal (improved or not improved); thus, we were unable to include the post-intervention scores in our analyses.
- The authors give the impression that none of the included participants died.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Blinded administration of interventions
Blinding of participants and personnel (performance bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of participants and personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear outcome data for participants who did not complete the trial. The trial does not appear to have post-randomisation exclusions although this is not specifically stated.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	Low risk	Not reported
Other bias	Low risk	No for-profit funding
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Dhiman 2000

Methods	Open, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 26 participants with cirrhosis and minimal hepatic encephalopathy. None had a past history of overt hepatic encephalopathy (see notes).

Dhiman 2000 *(Continued)*

	Age (mean ± SD) • Lactulose group 44.1 ± 18.0 years • Control group 47.8 ± 13.5 years Proportion of men • Lactulose group 85.7% • Control group 33.3% Aetiology of cirrhosis • Alcohol 36% • Hepatitis B 23%
Interventions	Lactulose syrup versus no intervention for 3 months
Outcomes	**Neuropsychiatric assessment** • Number Connection Tests A and B • Figure Connection Tests A and B • Block Design Test • Picture Completion Test
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, and adverse events assessed after 3 months
Inclusion period	Not reported
Country of origin	India
Notes	• The investigators screened 40 people with cirrhosis and no past history or current evidence of overt hepatic encephalopathy using a battery of psychometric tests. The trial includes the 26 participants diagnosed as having minimal hepatic encephalopathy on the basis of impaired performance on at least 2 of the 6 psychometric tests administered. These 26 participants received lactulose (n = 14) or no treatment (n = 12). The paper also provides data on the remaining 14 people who did not have minimal hepatic encephalopathy (6 of whom were tested at baseline and after 3 months). We included data for participants with minimal hepatic encephalopathy in our analyses. • The report provides the mean number of abnormal tests in the lactulose and control group post intervention. • The proportion of participants with Child's Grade B/C at baseline was 71% in the lactulose group and 67% in the control group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Numbered opaque sealed envelopes
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.

Dhiman 2000 *(Continued)*

Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. No blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised and include all participants randomised in the analyses. Missing outcome data unlikely to affect the analyses or be associated with the outcome.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	Low risk	Low risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Elkington 1969

Methods	Double-blind, cross-over, single-centre, outpatient trial
Participants	The trial includes 7 participants with cirrhosis and chronic hepatic encephalopathy (25%) or previous overt hepatic encephalopathy (75%). All participants had advanced decompensated liver disease. • Participant's characteristics are not reported (the paper states that participants had decompensated cirrhosis).
Interventions	Lactulose syrup versus placebo (sorbitol) for 15 days
Outcomes	**Neuropsychiatric assessment** • Mental status (modified Parson-Smith criteria) • Arterial blood ammonia • Electroencephalography
Outcomes included in meta-analyses	No outcomes included in our primary meta-analyses. Mortality and hepatic encephalopathy assessed after 15 days included in sensitivity analyses.
Inclusion period	Not reported
Country of origin	USA

Elkington 1969 *(Continued)*

Notes	• The trial describes 7 participants who were randomised to lactulose or placebo (sorbitol) and then after a wash-out period crossed over to the other treatment. We were unable to extract data on the individual treatment periods. We therefore excluded the trial from our analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Blinded allocation of interventions
Blinding of participants and personnel (performance bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of participants and personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No losses to follow-up or dropouts seemed to occur post-randomisation (clinical outcome data are presented for all participants). The trial report does not include information about the number of participants allocated to the intervention and control group during the first period.
Selective reporting (reporting bias)	Low risk	Predefined outcomes described
For-profit funding	High risk	A pharmaceutical company provided financial support
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Germain 1973

Methods	Double-blind, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 18 participants with cirrhosis who developed overt hepatic encephalopathy after portal-systemic shunt surgery.

Germain 1973 *(Continued)*

	Age (mean ± SD) • Lactulose group 47.0 ± 14.2 years • Control group 46.2 ± 16.6 years Proportion of men • Lactulose group 77.7% • Control group 66.6% Aetiology of cirrhosis not reported
Interventions	Lactulose syrup versus placebo (saccharose–based) for 15 days
Outcomes	**Neuropsychiatric assessment** • Mental state (modified Parson-Smith criteria) • Venous blood ammonia • Psychometric tests • Electroencephalography
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, and adverse events assessed after 15 days
Inclusion period	Not reported
Country of origin	France
Notes	Published in French

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of participants and personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome

Germain 1973 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised. There are no missing outcome data and no dropouts or losses to follow-up post-randomisation.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	High risk	A pharmaceutical company was involved in the trial.
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Grandi 1991

Methods	Open, cross-over, single-centre, inpatient trial
Participants	The trial includes 40 participants with cirrhosis and chronic hepatic encephalopathy Age (median) • Both groups 59.3 years Proportion of men • Both groups 62.5% Aetiology of cirrhosis • Not reported
Interventions	Crystalline lactulose versus lactitol for 60 days
Outcomes	**Neuropsychiatric assessment** • Modified Portal Systemic Encephalopathy Index comprising: a. Mental state (West Haven Criteria) b. Asterixis c. Number Connection Test A d. Venous blood ammonia
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, and adverse events (see notes) assessed after 60 days
Inclusion period	Not reported
Country of origin	Italy
Notes	• Published in Italian • All participants had Child's class B or C cirrhosis

Grandi 1991 *(Continued)*

- The trial does not describe the number of participants with or without an overall improvement in manifestations of hepatic encephalopathy, but describes the intervention effect using the overall score. We were therefore not able to include the trial in the analyses evaluating hepatic encephalopathy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. No blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised and there are no post-randomisation dropouts or losses to follow-up.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	High risk	Pharmaceutical companies supplied the interventions, but were not otherwise involved in the trial
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Heredia 1987

Methods	Open, parallel-arm, single-centre, inpatient trial
Participants	The trial includes 40 participants with cirrhosis and an acute episode of hepatic encephalopathy. In total, 65% had a previous history of overt hepatic encephalopathy.

Heredia 1987 *(Continued)*

	Age (mean ± SD) • Lactulose group 59.3 ± 3 years • Lactitol group 60.0 ± 3 years Proportion of men • Lactulose group 55% • Lactitol group 45% Aetiology of cirrhosis • Alcohol 48% • Hepatitis B/C not reported
Interventions	Lactulose syrup versus lactitol for 5 days
Outcomes	**Neuropsychiatric assessment** • Mental state (modified Conn Scale) • Number Connection Test A • Venous blood ammonia • Electroencephalography
Outcomes included in meta-analyses	Mortality, adverse events, and blood ammonia assessed after 5 days
Inclusion period	Not reported
Country of origin	Spain
Notes	4 participants (10%) had undergone portal systemic shunt surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Numbered, sealed envelopes
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. No blinding of outcome assessment.
Blinding of outcome assessment (detection bias)	Unclear risk	Detection bias unlikely to influence the outcome

Heredia 1987 *(Continued)*
Mortality

Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised and there are no post-randomisation dropouts or losses to follow-up.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	High risk	A pharmaceutical company supplied the study drugs, but were not otherwise involved in the trial.
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Heredia 1988

Methods	Open, cross-over, single-centre, outpatient trial
Participants	The trial includes 20 participants with cirrhosis and previous portal-systemic shunt surgery with chronic hepatic encephalopathy Age (mean ± SD) • Both groups 54.5 ± 2.1 years Proportion of men • Both groups 70% Aetiology of cirrhosis • Alcohol 60% • Hepatitis B/C 24%
Interventions	Lactulose syrup versus lactitol for 3 months
Outcomes	**Neuropsychiatric assessment** • Quantified neurological status • Portal Systemic Encephalopathy Sum and Index comprising: a. Mental state (West Haven Criteria) b. Asterixis c. Number Connection Test A d. Venous blood ammonia e. Electroencephalogram
Outcomes included in meta-analyses	Mortality and adverse events assessed after 3 months (see notes)
Inclusion period	Not reported

Heredia 1988 *(Continued)*

Country of origin	Spain
Notes	• The trial includes 25 participants. 2 died and 3 dropped out of the study. The trial report does not provide information about the allocation arm (lactulose or lactitol) of the participants who dropped out. • The authors reports the effect on hepatic encephalopathy using the overall Portal Systemic Encephalopathy Sum, but do not describe the number of participants with (or without) an overall improvement in hepatic encephalopathy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Numbered, sealed envelopes
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. No blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants who died or dropped out are excluded from the analyses
Selective reporting (reporting bias)	High risk	Mortality data incomplete
For-profit funding	High risk	A pharmaceutical company supplied lactitol, but was not otherwise involved in the trial
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Horsmans 1997

Methods	Double-blind, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 14 participants with cirrhosis and minimal hepatic encephalopathy. None of the included participants had a history of overt hepatic encephalopathy. Age (mean ± SD) • Lactulose group 59.0 ± 8.7 years • Control group 56.1 ± 14.2 years Proportion of men • Lactulose group 42.9% • Control group 57.1% Aetiology of cirrhosis • Alcohol 35.7% • Hepatitis B/C not reported
Interventions	Crystalline lactulose versus placebo (lactose) for 15 days
Outcomes	**Neuropsychiatric assessment** • Number Connection Test A • Race Track Test • Automated sinusoid and psychomotor tests • Electroencephalography
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, adverse events, and Number Connection Test results assessed after 15 days
Inclusion period	Not reported
Country of origin	Belgium
Notes	• Participants were not lactose intolerant • The criteria for the diagnosis of minimal hepatic encephalopathy were not specified; all participants were clinically normal and had normal electroencephalograms, but had impaired psychometric performance.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Numbered sealed envelopes.
Blinding of participants and personnel (performance bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of participants and personnel.
Blinding of participants and personnel (performance bias)	Low risk	Performance bias unlikely to influence the outcome

Horsmans 1997 *(Continued)*

Mortality		
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised. All participants completed the trial.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	High risk	A pharmaceutical company supplied the interventions, but was not otherwise involved in the trial.
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Jain 2013

Methods	Open, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 60 participants with cirrhosis and minimal hepatic encephalopathy Age (median and range) • Lactulose group 42 (15 to 70) years • Control group 41 (17 to 68) years Proportion of men • Lactulose group 66.7% • Control group 63.3% Aetiology of cirrhosis • Alcohol 58.3% • Hepatitis B 18.3% • Hepatitis C 15.0%
Interventions	Lactulose syrup versus no intervention for 3 months
Outcomes	**Neuropsychiatric assessment** • Mental status (West Haven Criteria) • Arterial blood ammonia • Psychometric Hepatic Encephalopathy Score (PHES) comprising:

Jain 2013 *(Continued)*

a. Number Connection Tests A and B
b. Digit symbol test
c. Serial dotting test
d. Line drawing test

Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, and adverse events assessed after 3 months
Inclusion period	October 2011 to February 2012
Country of origin	India
Notes	• The investigators used the Psychometric Hepatic Encephalopathy Score to diagnose minimal hepatic encephalopathy. • The paper also includes follow-up data on 20 participants who did not have evidence of minimal hepatic encephalopathy. • The median (range) Model of End-stage Liver Disease score at inclusion was 19 (14 to 34) for the lactulose and 20 (14 to 32) for the control group. • The paper also describes plasma cytokines and cerebral magnetic resonance spectroscopy, which are not included in our analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. This trial is registered on clinicaltrials.gov as placebo-controlled, but is conducted and reported as an open trial in which the control group received no intervention. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	No blinding of outcome assessment
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	The investigators account for all participants randomised. 2 participants were lost to follow-up and excluded from the analyses.
Selective reporting (reporting bias)	High risk	In the trial registration, the primary outcome measure was 'improvement of minimal hepatic encephalopathy'. In the published report the primary outcome was the change in arterial blood ammonia, inflammatory mediators, serum endotoxins, and cerebral magnetic resonance spectroscopy. The pub-

Jain 2013 *(Continued)*

		lished report describes "improvement in minimal hepatic encephalopathy" as a secondary outcome measure (reported for participants receiving lactulose).
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Jankovic 1996

Methods	Open, parallel-arm, single-centre, inpatient trial
Participants	The trial includes 16 participants with cirrhosis admitted with an acute episode of hepatic encephalopathy. Participant characteristics not reported.
Interventions	Lactulose syrup versus lactitol for 5 to 7 days
Outcomes	**Neuropsychiatric assessment** • Mental status (West Haven Criteria) • Number Connection Test A • Electroencephalography
Outcomes included in meta-analyses	Mortality and adverse events assessed after 5 to 7 days and 13 days after the end of treatment (see notes)
Inclusion period	Not reported
Country of origin	Serbia
Notes	• The authors reported the intervention effect on the mean values for the measured variables, but did not report the number with (or without) overall improvement in hepatic encephalopathy. We were therefore unable to include the data in our analysis for the outcome hepatic encephalopathy.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.

Jankovic 1996 *(Continued)*

Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. No blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants with missing outcome data are not described and the analyses do not account for participants with missing outcome data.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Li 1999

Methods	Open, parallel-arm, multicentre, outpatient trial
Participants	The trial includes 86 participants with cirrhosis and minimal hepatic encephalopathy (see notes). Age (mean ± SD) • Lactulose group 47.6 ± 10.9 years • Control group 41.5 ± 13.0 years Proportion of men • Lactulose group 77.1% • Control group 89.5% Aetiology of cirrhosis not reported
Interventions	Lactulose syrup versus no intervention for 30 days
Outcomes	**Neuropsychiatric assessment** • Number Connection Test A • Digit Symbol Test

Li 1999 *(Continued)*

Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, and adverse events assessed after 30 days
Inclusion period	January 1997 to January 1998
Country of origin	China
Notes	• Published in Chinese • The participants had minimal hepatic encephalopathy diagnosed on the basis of impaired performance on the Number Connection Test results or Digit Symbol Test • The proportion of participants with Child's Grades B/C in the lactulose group was 79.2% and in the control group 84.2%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. No blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised. All participants completed the trial.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

McClain 1984

Methods	Double-blind, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 32 participants with cirrhosis and minimal hepatic encephalopathy (see notes). Age (mean ± SD) • Lactulose group 55 ± 6.5 years • Control group 54.0 ± 9.1 years Proportion of men • Both groups 96.9% Aetiology of cirrhosis • Alcohol 100%
Interventions	Lactulose syrup versus placebo (sucrose) for 3 months
Outcomes	**Neuropsychiatric assessment** • Number Connection Tests A and B • Digit Symbol Test • Speed of writing words • Speed of writing numbers
Outcomes included in meta-analyses	Adverse events assessed after 3 months (see notes)
Inclusion period	Not reported
Country of origin	USA
Notes	• All included participants had minimal hepatic encephalopathy (psychometric testing shows impaired cognitive function). • The report describes the characteristics of participants who completed the trial (lactulose 10 participants, placebo 12). • The investigators assessed the quality of life based on the Katz social functioning score. The publication does not include quantitative data, but the authors comment that they saw no changes in the Katz score in response to treatment. • We were unable to gather data on the number with (or without) improvement in hepatic encephalopathy because the results are expressed as percentage change over baseline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Central independent unit
Blinding of participants and personnel (performance bias)	Low risk	Double-blind, placebo-controlled. Blinding of participants and personnel.

McClain 1984 *(Continued)*

Non-mortality outcomes		
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	The paper does not account for participants who did not complete the trial and the analyses exclude participants with missing outcome data.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	High risk	A pharmaceutical company supplied the interventions, but was not otherwise involved in the trial.
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Mittal 2011

Methods	Open, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 80 participants with cirrhosis and minimal hepatic encephalopathy Age (mean ± SD) • Lactulose group 43.9 ± 10.9 years • Control group 41.2 ± 11.9 years Proportion of men • Lactulose group 80% • Control group 75% Aetiology of cirrhosis • Alcohol 37.5% • Hepatitis B/C 35.0%
Interventions	Lactulose syrup versus no intervention for 3 months
Outcomes	**Neuropsychiatric assessment**

Mittal 2011 *(Continued)*

- Mental status (West Haven Criteria)
- Number Connection Tests A and B
- Figure Connection Tests A and B
- Picture Completion Test
- Block Design Test
- Arterial blood ammonia

Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, adverse events, quality of life, and blood ammonia concentration assessed after 3 months
Inclusion period	October 2007 to October 2009
Country of origin	India
Notes	• The trial includes 160 participants randomised to lactulose (n = 40), probiotics (n = 40), L-ornithine L-aspartate (n = 40), or no treatment (n = 40). The L-ornithine L-aspartate and probiotic groups are not included in our analyses. • The investigators based the diagnosis of minimal hepatic encephalopathy on the presence of at least 2 abnormal psychometric tests. They expressed the psychometric test results as a Z score equating to the difference between the observed result and the population norm. They defined a Z score of <-2 as abnormal. • The investigators assessed quality of life with the Sickness Impact Profile questionnaire, which assessed the influence of disease and treatment on daily functioning. The questionnaire consists of 136 items, which are grouped into 12 scales such as sleep and rest, eating, work, and home management. Scores range from 0 (best score) to 100 (worst score). Changes in the score were calculated. The scores were comparable at baseline. After treatment, the score was lower in the lactulose group compared with controls.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. No blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias)	Low risk	The investigators account for all participants randomised and used sufficient methods to handle missing data in the analyses of clinical outcomes (but not

Mittal 2011 *(Continued)*

All outcomes		in the analyses of surrogate outcomes). Missing outcome data are unlikely to affect the analyses or to be associated with the outcome.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	Low risk	Low risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Morgan 1987a

Methods	Double-blind, parallel-arm, single-centre, inpatient trial
Participants	The trial includes 25 participants with cirrhosis and acute hepatic encephalopathy (see notes). Age (mean ± SD) • Lactulose group 48.3 ± 15.8 years • Lactitol group 48.4 ± 12.5 years Proportion of men • Lactulose group 46.7% • Lactitol group 61.5% Aetiology of cirrhosis • Alcohol 53.7% • Hepatitis B/C 0%
Interventions	Lactulose versus lactitol as identically presented liquids for 5 days
Outcomes	**Neuropsychiatric assessment** • Portal Systemic Encephalopathy Sum and Index comprising: a. Mental state (West Haven Criteria) b. Asterixis c. Number Connection Test A d. Venous blood ammonia e. Electroencephalogram
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, adverse events, and Number Connection Test results assessed after 5 days (end of treatment). Additional information retrieved for clinical outcomes 1 month after the end of treatment (see notes).
Inclusion period	July 1984 to December 1985
Country of origin	United Kingdom

Morgan 1987a *(Continued)*

Notes	• Initially, the investigators evaluated 27 potentially eligible participants, but excluded 2 with fulminant hepatic failure before treatment. The investigators randomised 25 participants, who experienced between them 28 episodes of hepatic encephalopathy. • 3 participants discontinued treatment with lactitol because they developed severe nausea (n = 1), profuse gastrointestinal bleeding (n = 1), or ileus (n = 1). All 3 participants died after the end of treatment. • None of the participants died during the trial. Participants who died after the completion of the trial had severely decompensated cirrhosis. • The investigators reported that the time to improved manifestations of hepatic encephalopathy was shorter in the group of participants allocated to lactitol. • Participants with autoimmune hepatitis made up 23.1% of the lactulose group and 13.3% of the lactitol group. • All participants had Child's Grade B/C cirrhosis. • One of the review authors (Marsha Y Morgan) was the primary investigator on the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Central independent unit
Blinding of participants and personnel (performance bias) Non-mortality outcomes	Low risk	Double-blind trial with administration of the interventions as identically appearing solutions. Blinding of participants and personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Blinding of outcome assessment
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised. There are no post-randomisation exclusions (follow-up assessments and clinical monitoring continued for all participants, including those who discontinued the interventions).
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	High risk	A pharmaceutical company supplied lactitol, but was not otherwise involved in the trial.
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk

Morgan 1987a *(Continued)*

Overall assessment (non-mortality outcomes)	High risk	High risk

Morgan 1987b

Methods	Double-blind, cross-over, single-centre, outpatient trial
Participants	The trial includes 12 participants with cirrhosis and chronic hepatic encephalopathy. Age (mean ± SD) • Both groups 57.3 ± 11.5 years Proportion of men • Both groups 55.6% Aetiology of cirrhosis • Alcohol 44% • Hepatitis B/C 0%
Interventions	Lactulose versus lactitol as identically presented liquids for 3 months
Outcomes	**Neuropsychiatric assessment** • Portal Systemic Encephalopathy Sum and Index comprising: a. Mental status (West Haven Criteria) b. Asterixis c. Number Connection Test A d. Venous blood ammonia e. Electroencephalogram
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, adverse events, Number Connection Test results, and blood ammonia concentrations assessed after 3 months
Inclusion period	November 1985 to February 1986
Country of origin	United Kingdom
Notes	• 3 of 9 participants had surgical portal-systemic shunts. • In total, 56% of participants had cryptogenic cirrhosis. • 3 of 12 participants did not complete the trial because they died (n = 1) or began to abuse alcohol and were non-compliant in the early phase of the first treatment period (n = 2). Data on all participants are included in our analyses. • One of the review authors (Marsha Y Morgan) was primary investigator on the trial.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table

Morgan 1987b *(Continued)*

Allocation concealment (selection bias)	Low risk	Central independent unit
Blinding of participants and personnel (performance bias) Non-mortality outcomes	Low risk	Double-blind trial with administration of the interventions as identically appearing solutions. Blinding of participants and personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Blinding of outcome assessment
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised and there are no missing outcome data.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	High risk	A pharmaceutical company supplied lactitol, but was not otherwise involved in the trial.
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Morgan 1989

Methods	Single-blind, cross-over, single-centre, outpatient trial
Participants	The trial includes 20 participants with cirrhosis, minimal hepatic encephalopathy, and no history of previous overt hepatic encephalopathy (see notes). Age (mean and range) • Both groups 52.0 (37 to 66) years Proportion of men • Both groups 78.6% Aetiology of cirrhosis • Alcohol 100%

Morgan 1989 *(Continued)*

Interventions	Lactulose syrup versus lactitol for 2 months.
Outcomes	**Neuropsychiatric assessment** • Mental status (Modified Conn Score) • Number Connection Tests A and B • Digit Symbol Test • Digit Copying Test • Computer-based visual reaction time • Computer-based perceptual maze test • Electroencephalography
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, adverse events, and Number Connection Test results assessed after 2 months
Inclusion period	October 1986 to April 1988
Country of origin	United Kingdom
Notes	• All participants were abstinent from alcohol. • 6 of the initially randomised participants did not complete 2 weeks of treatment because of non-serious adverse events (lactitol n = 1) or for reasons unrelated to the trial (lactulose: n = 2; lactitol: n = 3). 14 participants completed the trial. None died. We included data on all randomised participants in our analyses. • One of the review authors (Marsha Y Morgan) was the primary investigator on the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open, single-blind trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Open, single-blind trial. Blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised and there are no missing outcome data.

Morgan 1989 *(Continued)*

Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	High risk	A pharmaceutical company supplied lactitol, but was not otherwise involved in the trial.
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Pai 1995

Methods	Single-blind, parallel-arm, single-centre, inpatient trial
Participants	The trial includes 41 participants with cirrhosis and acute hepatic encephalopathy. Age (mean ± SD) • Lactulose group 65.9 ± 9.8 years • Lactitol group 67.5 ± 4.9 years Proportion of men • Lactulose group 75.0% • Lactitol group 95.0% Aetiology of cirrhosis • Alcohol 18%. • Hepatitis B/C 69%
Interventions	Lactulose syrup versus lactitol for 5 days
Outcomes	**Neuropsychiatric assessment** • Portal Systemic Encephalopathy Sum and Index comprising: a. Mental state (West Haven Criteria) b. Asterixis c. Number Connection Test A d. Venous blood ammonia e. Electroencephalogram
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, and adverse events assessed after 5 days
Inclusion period	April 1993 to April 1994
Country of origin	Taiwan
Notes	All participants had Child's Grade B/C cirrhosis
Risk of bias	

Pai 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open, single-blind trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Open, single-blind trial. Blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	The investigators account for all participants randomised, but do not include participants who died or dropped out in the reported analyses.
Selective reporting (reporting bias)	High risk	The trial report does not include information about the allocation group of participants who died within the first 5 days after randomisation.
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Prasad 2007

Methods	Open, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 61 participants with cirrhosis and minimal hepatic encephalopathy (see notes). Age (mean and range) • Lactulose group 48.3 (38.4 to 58.2) years • Control group 50.6 (39.1 to 62.1) years Proportion of men • Lactulose group 87.1%

Prasad 2007 *(Continued)*

	• Control group 93.3% Aetiology of cirrhosis • Alcohol 65% • Hepatitis B/C 30%
Interventions	Lactulose syrup versus no intervention for 3 months
Outcomes	**Neuropsychiatric assessment** • Mini Mental State Examination • Mental status (West Haven Criteria) • Number Connection Tests A and B • Figure Connection Tests A and B • Picture Completion Test • Block Design Test
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, adverse events, and quality of life assessed after 3 months
Inclusion period	January 2004 to March 2005
Country of origin	India
Notes	• The investigators based the diagnosis of minimal hepatic encephalopathy on the presence of at least 2 abnormal psychometric tests. They expressed the psychometric test results as a Z score equating to the difference between the observed result and the population norm. They defined a Z score of <-2 as abnormal. The investigators calculated a mean Z score (mZS) for each patient and referred to changes in the number of abnormal tests AbnNP and the mZS at the end of treatment or follow-up as ΔAbnNP and ΔmZS • The proportion with Child's Grade B/C was 66.7% in the lactulose group and 55.2% in the control group. • The investigators describe 29 participants who were neuropsychiatrically unimpaired and followed them for 3 months in the same way as the participants in the randomised clinical trial. • The investigators assessed the quality of life based on the Sickness Impact Profile. They defined the change in the total score after follow-up as the estimated change in the overall quality of life. At baseline, participants with minimal hepatic encephalopathy had impairment in 11 of the 12 scales in the score (in particular the social interaction, alertness, emotional behaviour, sleep, work, home management, recreation and pastime).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.

Prasad 2007 *(Continued)*

Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. No blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised and used sufficient methods to handle missing data in the analyses of clinical outcomes. 5 participants in the control group and none in the lactulose group were lost to follow-up. Missing outcome data are unlikely to affect the analyses or to be associated with the outcome.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	Low risk	Low risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Quero 1997

Methods	Double-blind, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 40 participants with cirrhosis and minimal hepatic encephalopathy. Age (mean ± SD) • Lactulose group 51.9 ± 13.0 years • Control group 49.7 ± 12 years Proportion of men • Lactulose group 73.7% • Control group 71.4% Aetiology of cirrhosis • Alcohol 27.5% • Hepatitis B/C 30.0%
Interventions	Crystalline lactulose versus placebo (lactose) for 6 months
Outcomes	**Neuropsychiatric assessment**

Quero 1997 *(Continued)*

- Mental status (criteria not specified)
- Number Connection Test A
- Symbol Digit Test
- Electroencephalogram
- Arterial ammonia concentration

Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, adverse events, and quality of life assessed after a maximum of 9 months (3 months after the end of therapy)
Inclusion period	October 1992 to September 1994
Country of origin	Holland
Notes	• The investigators diagnosed participants with at least 2 abnormal psychometric tests scores as having minimal hepatic encephalopathy. • All participants had elevated blood ammonia levels. • Proportion with Child's Grade B/C was 21.0% in the lactulose group and 9.5% in the control group. • The investigators assessed quality of life using the Sickness Impact Profile and defined the change in the total score after follow-up as the estimated change in the overall quality of life. At baseline, participants with minimal hepatic encephalopathy had impairment in 11 of the 12 scales in the score (in particular social interaction, alertness, emotional behaviour, sleep, work, home management, recreation and pastime).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Centrally prepared, numbered drug containers
Blinding of participants and personnel (performance bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of participants and personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	The investigators account for all participants randomised, but the trial report excludes participants with missing outcomes (2 from both intervention groups) from the analyses.
Selective reporting (reporting bias)	Low risk	Predefined outcomes not reported

Quero 1997 *(Continued)*

For-profit funding	High risk	The trial received funding from a pharmaceutical company
Other bias	Low risk	No other biases identified
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Raza 2004

Methods	Open, parallel-arm, single-centre, inpatient trial
Participants	The trial includes 31 participants with cirrhosis experiencing an acute episode of hepatic encephalopathy. Age (mean) • Lactulose group 55.1 years • Control group 52.4 years Proportion of men • Lactulose group 27.8%. • Control group 46.2%. Aetiology of cirrhosis • Hepatitis B/C 100%
Interventions	Lactulose enemata versus tap water enemata administered for a mean of 4.5 days depending on clinical response
Outcomes	**Neuropsychiatric assessment** • Clinical scoring (Jones and Gammal) • Portal Systemic Encephalopathy Sum and Index comprising: a. Mental state (West Haven Criteria) b. Asterixis c. Digit Symbol Test (replacing Number Connection Test A) d. Venous blood ammonia e. Electroencephalogram
Outcomes included in meta-analyses	Mortality and hepatic encephalopathy assessed after a mean duration of 4.5 days
Inclusion period	Not reported
Country of origin	Pakistan
Notes	• The primary outcome was the time to improvement. • The investigators made the assessments at 48 hours and then at the end of treatment, which was on average 4.5 days. • Both allocation groups also received oral lactulose syrup.

Raza 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The investigators described the allocation as 1:1, but the allocation sequence generation is unclear.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. No blinding of the outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participants who were excluded or lost to follow-up are not described. The handling of participants with missing outcomes is unclear.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	High risk	A pharmaceutical company supplied the drug, but was not otherwise involved in the trial.
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Riggio 1989

Methods	Single-blind, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 31 participants with cirrhosis who had undergone portal-systemic shunt surgery and evaluates the prevention of hepatic encephalopathy. In total, 46.7% in the lactulose group and 37.5% in the lactitol group had experienced at least 1 episode of hepatic encephalopathy within 1 year of inclusion of the trial. Age (mean ± SD)

Riggio 1989 *(Continued)*

- Lactulose group 49 ± 13 years
- Lactitol group 59 ± 6 years

Proportion of men

- Lactulose group 73.3%
- Lactitol group 68.8%

Aetiology of cirrhosis

- Alcohol 19%
- Hepatitis B/C 19%

Interventions	Lactulose syrup versus lactitol for 6 months
Outcomes	**Neuropsychiatric assessment** • Portal Systemic Encephalopathy Sum and Index comprising: a. Mental state (West Haven Criteria) b. Asterixis c. Number Connection Test A d. Venous blood ammonia e. Electroencephalogram
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, and adverse events assessed after 6 months
Inclusion period	Not described
Country of origin	Italy
Notes	• The proportion of participants with Grade B/C cirrhosis was 13.3% in the lactulose and 12.5% in the control group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open, single-blind trial. No blinding of participants and personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Open, single-blind trial. Blinding of outcome assessment.

Riggio 1989 *(Continued)*

Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised; there are no missing outcome data and all participants are included in the analyses.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	High risk	A pharmaceutical company supplied the lactitol, but was not otherwise involved in the trial.
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Riggio 2005

Methods	Single-blind, parallel-arm, single-centre, inpatient/outpatient trial
Participants	The trial includes 50 participants with cirrhosis randomised immediately after transjugular intrahepatic portosystemic shunt (TIPS) placement. 15% (8% in the lactitol group and 24% in the control group) had experienced a previous episode of hepatic encephalopathy. Age (mean ± SD) • Lactitol group 60.6 ± 9.0 years • Control group 54.9 ± 11.7 years Proportion of men • Lactitol group 56% • Control group 84% Aetiology of cirrhosis • Alcohol 34% • Hepatitis B/C not reported.
Interventions	Lactitol versus no intervention for 6 months
Outcomes	**Neuropsychiatric assessment** • Portal Systemic Encephalopathy Sum and Index comprising: a. Mental state (West Haven Criteria) b. Asterixis c. Number Connection Test A d. Venous blood ammonia e. Electroencephalogram

Riggio 2005 *(Continued)*

Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, adverse events, and blood ammonia concentrations assessed after 6 months
Inclusion period	November 1998 to September 2003
Country of origin	Italy
Notes	• The trial includes 75 participants randomised to no treatment (n = 25), lactitol (n = 25), or rifaximin (n = 25). The rifaximin group is not included in our analyses. • The proportion of participants with Child's B/C cirrhosis was 76% in the lactitol group and 64% in the control group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants and personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Open, single-blind trial. Blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised and used sufficient methods to handle missing data. Missing outcome data are unlikely to affect the analyses or to be associated with the outcome.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	Low risk	Low risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Rodgers 1973

Methods	Double-blind, cross-over, single-centre, outpatient trial
Participants	The trial includes 6 participants with cirrhosis and chronic hepatic encephalopathy. 3 are described in detail. Age (mean) • Both groups: 65 years Proportion of men • Both groups: 66% Aetiology of cirrhosis not reported
Interventions	Lactulose syrup versus placebo (sorbitol) (see notes)
Outcomes	**Neuropsychiatric assessment** • Clinical grading (criteria not described) • Blood ammonia • Electroencephalography
Outcomes included in meta-analyses	None (see notes)
Inclusion period	1967 to 1970
Country of origin	USA
Notes	• The investigators randomised 6 participants to treatment with lactulose or placebo (sorbitol) alternatively for 2-month periods. The paper describes 3 of these participants in detail. We were unable to extract quantitative data from the trial publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Centrally prepared, numbered drug containers
Blinding of participants and personnel (performance bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of participants and personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of outcome assessment.

Rodgers 1973 *(Continued)*

Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	The investigators do not account for all participants randomised in the trial report or analysis.
Selective reporting (reporting bias)	High risk	Predefined outcomes not reported
For-profit funding	High risk	A pharmaceutical company supported the trial with a grant and supplied the drug and placebo.
Other bias	Low risk	No other biases identified
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Sharma 2009

Methods	Open, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 140 participants with cirrhosis who had recovered from an episode of overt hepatic encephalopathy. The trial evaluates secondary prevention. In total, 57% of included participants had minimal hepatic encephalopathy. Age (mean ± SD) • Lactulose group 48.2 ± 8.4 years • Control group 44.9 ± 10.2 years Proportion of men • Lactulose group 77.1% • Control group 71.4% Aetiology of cirrhosis • Alcohol 39.2% • Hepatitis B/C 39.2%
Interventions	Lactulose syrup versus no intervention for 12 months
Outcomes	**Neuropsychiatric assessment** • Mental status (West Haven Criteria) • Number Connection Tests A and B • Figure Connection Tests A and B • Digit Symbol Test • Object Assembly Test • Critical flicker frequency

Sharma 2009 *(Continued)*

Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, and adverse events assessed after 12 months
Inclusion period	January 2006 to June 2008
Country of origin	India
Notes	• The investigators defined the primary endpoint as the development of an episode of overt hepatic encephalopathy 6 months after randomisation. • The Model for End-Stage Liver Disease (MELD) score (mean ± SD) at inclusion was 21.8 ± 3.4 in the lactulose group and 20.6 ± 2.4 in the control group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. The investigators describe the trial as placebo-controlled, but the placebo intervention is not described in the methods section describes the trial as open. No blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	Open trial. The investigators describe the trial as placebo-controlled in the trial registry, but the placebo intervention is not mentioned in the methods section of the published RCT. No blinding of outcome assessment.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	Low risk	Low risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Sharma 2011

Methods	Open, parallel-arm, single-centre, inpatient trial
Participants	The trial includes 70 participants with cirrhosis who were stable after an acute variceal bleed. In total, the trial included 16% with a previous episode of hepatic encephalopathy (17.1% in the lactulose group and 14.3% in the control group). The trial evaluates prevention of hepatic encephalopathy. Age (mean ± SD) • Lactulose group 41.6 ± 12.9 years • Control group 37.2 ± 16.0 years Proportion of men • Lactulose group 86% • Control group 80% Aetiology of cirrhosis • Alcohol 47% • Hepatitis B/C 37%
Interventions	Lactulose syrup versus no intervention for 120 hours
Outcomes	**Neuropsychiatric assessment** • Mental state (West Haven Criteria) • Arterial blood ammonia
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, and adverse events assessed after 120 hours
Inclusion period	December 2008 to January 2010
Country of origin	India
Notes	• The trial report describes the blood ammonia concentrations for participants who did not did not develop hepatic encephalopathy, but not the values for participants in the 2 allocation groups. • The Model for End-Stage Liver Disease (MELD) score (mean ± SD) at inclusion was 16.7 ± 5.7 in the lactulose group and 15.8 ± 3.8 in the control group.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Serially numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.

Sharma 2011 *(Continued)*

Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. No blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised. There are no participants with post-randomisation missing outcome data.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	Low risk	Low risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Sharma 2012

Methods	Open, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 120 participants with cirrhosis and no history of overt hepatic encephalopathy. Of these, 57% had minimal hepatic encephalopathy at inclusion. The trial evaluates prevention of hepatic encephalopathy. Age (mean ± SD) • Lactulose group 43.4 ± 12.5 years • Control group 42.2 ± 11.5 years Proportion of men • Lactulose group 80.0% • Control group 88.3% Aetiology of cirrhosis • Alcohol 30.8% • Hepatitis B 30.0% • Hepatitis C 12.5%
Interventions	Lactulose syrup versus no intervention for 12 months
Outcomes	**Neuropsychiatric assessment**

Sharma 2012 *(Continued)*

- Mental status (West Haven Criteria)
- Number Connection Tests A and B
- Figure Connection Tests A and B
- Picture Completion Test
- Digit Symbol Test
- Serial Dotting Test
- Line Tracing Test
- Critical flicker frequency

Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, and adverse events assessed after 12 months
Inclusion period	January 2008 to September 2009
Country of origin	India
Notes	• The investigators based the diagnosis of minimal hepatic encephalopathy on the finding of 2 or more abnormal psychometric tests. • The investigators switched 4 participants from the control to the intervention group. These participants are included in their original allocation group in our analyses. • The Model for End-Stage Liver Disease (MELD) score (mean ± SD) at inclusion was 13.4 ± 4.8 in the lactulose group and 12.3 ± 4.8 in the control group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. No blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised and used sufficient methods to handle missing data. Missing outcome data are unlikely to affect the analyses or to be associated with the outcome.
Selective reporting (reporting bias)	Low risk	Predefined outcomes are reported

Sharma 2012 *(Continued)*

For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	Low risk	Low risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Shi 1997

Methods	Double-blind, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 31 participants with cirrhosis and minimal hepatic encephalopathy. Mean age • Both groups 54 years Proportion of men • Both groups 87% Aetiology of cirrhosis • Alcohol 0% • Hepatitis B/C not described
Interventions	Lactitol versus placebo (glucose) for 2 weeks
Outcomes	**Neuropsychiatric assessment** • Number Connection Test • Digit Symbol Test • Somatosensory evoked potentials • Blood ammonia
Outcomes included in meta-analyses	No outcomes (see notes)
Inclusion period	Not reported
Country of origin	China
Notes	• The authors do not describe the criteria used to diagnose minimal hepatic encephalopathy. • No numerical data are provided. • Published in Chinese.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described

Shi 1997 *(Continued)*

Allocation concealment (selection bias)	Low risk	Administration of coded, identical drug containers
Blinding of participants and personnel (performance bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of participants and personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Patient with missing outcome data are not described and the handling of participants with missing outcomes in the analyses is unclear.
Selective reporting (reporting bias)	High risk	Predefined outcomes not reported
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Simmons 1970

Methods	Double-blind, parallel-arm, single-centre, inpatient trial
Participants	The trial includes 26 participants with cirrhosis and acute hepatic encephalopathy Age (mean ± SD) Lactulose group 50.4 ± 7.6 years Control group 51.8 ± 6.7 years Proportion of men • Both groups 100% Aetiology of cirrhosis • Alcohol 100%

Simmons 1970 *(Continued)*

Interventions	Lactulose syrup versus placebo (glucose) for 10 days
Outcomes	**Neuropsychiatric assessment** • Mental function tests (Sherlock) • Venous blood ammonia
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, and adverse events assessed after 10 days
Inclusion period	Not reported
Country of origin	USA
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of participants and personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised. There are no missing outcomes and all participants are included in the analyses.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	High risk	A pharmaceutical company supplied lactulose, but was not otherwise involved in the trial.
Other bias	Low risk	No other biases

Simmons 1970 *(Continued)*

Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Uribe 1987a

Methods	Double-blind, cross-over, single-centre, inpatient trial
Participants	The trial includes 37 participants with cirrhosis and acute hepatic encephalopathy Participant characteristics not reported
Interventions	Rectal lactitol enemata versus rectal placebo enemata (lactose or tap water) for 4 days
Outcomes	N**europsychiatric assessment** • Portal Systemic Encephalopathy Sum and Index comprising: a. Mental state (West Haven Criteria) b. Asterixis c. Number Connection Test A d. Venous blood ammonia e. Electroencephalogram
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, adverse events, Number Connection Test results, and blood ammonia concentrations assessed after 4 days
Inclusion period	Not reported
Country of origin	Mexico
Notes	• The trial includes 37 participants with cirrhosis experiencing 45 episodes of acute overt hepatic encephalopathy. • The investigators undertook a pre-agreed group sequential analysis of response after randomisation of the first 20 participants to enemata of lactitol (n = 10), lactose (n = 5), or tap water (n = 5). The investigators discontinued the tap water arm because the mortality rate was high; the trial continued with the randomisation of participants to lactitol or lactose. • In our analyses, we combined participants randomised to the tap water and lactose groups (n = 23). • None of the participants in the trial was lactose intolerant.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Blinded administration of coded drug containers
Blinding of participants and personnel (performance bias)	Low risk	Double-blind, placebo-controlled. Blinding of participants and personnel.

Uribe 1987a *(Continued)*

Non-mortality outcomes		
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised and there are no missing outcome data.
Selective reporting (reporting bias)	Low risk	Predefined outcomes are described
For-profit funding	High risk	One of the trial investigators was an employee of a pharmaceutical company, which manufactured the trial drug.
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Uribe 1987b

Methods	Double-blind, cross-over, single-centre, outpatient trial
Participants	The trial includes 20 participants with cirrhosis and chronic hepatic encephalopathy. Age (mean ± SD) • Lactitol group 41.0 ± 1.5 years • Control group 40.8 ± 2.5 years Proportion of men • Lactitol group 62.5% • Control group 40.0% Aetiology of cirrhosis • Alcohol 44% • Hepatitis B/C 55%
Interventions	Lactitol versus placebo (lactose) for 2 weeks
Outcomes	N**europsychiatric assessment**

Uribe 1987b *(Continued)*

- Portal Systemic Encephalopathy Sum and Index comprising:
  a. Mental state (West Haven Criteria)
  b. Asterixis
  c. Number Connection Test A
  d. Venous blood ammonia
  e. Electroencephalogram

Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, adverse events, Number Connection Test results, and blood ammonia concentrations assessed after 2 weeks
Inclusion period	Not reported
Country of origin	Mexico
Notes	None of the participants in the control group was lactose intolerant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Blinded administration of coded drug containers
Blinding of participants and personnel (performance bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of participants and personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Double-blind, placebo-controlled. Blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	The investigators account for all participants randomised. There are no missing data for clinical outcomes, but trial authors exclude 2 participants from the reported analyses. The 2 participants developed complications requiring antibiotics and never received the trial medication.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	High risk	One of the trial investigators was an employee of a pharmaceutical company, which manufactured the trial drug.
Other bias	Low risk	No other biases

Uribe 1987b *(Continued)*

Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Watanabe 1997

Methods	Open, parallel-arm, multicentre, outpatient trial
Participants	The trial includes 75 participants with cirrhosis and previous overt hepatic encephalopathy. In total, 48% had minimal hepatic encephalopathy and 52% were unimpaired based on neuropsychiatric assessment. Age (mean ± SD) • Lactulose group (unimpaired) 56.7 ± 9.5 years • Control group (unimpaired) 58.6 ± 6.2 years • Lactulose group (minimal hepatic encephalopathy) 62.0 ± 7.3 years • Control group (minimal hepatic encephalopathy) 65.6 ± 7.1 years Proportion of men • Lactulose and control group (unimpaired) 62% • Lactulose and control group (minimal hepatic encephalopathy) 47% Aetiology of cirrhosis • Alcohol 11% • Hepatitis B/C 78%
Interventions	Lactulose syrup versus no intervention for 8 weeks (see notes)
Outcomes	**Neuropsychiatric assessment** • Mental state (Conn) • Number Connection Test part A • Symbol Digit Test • Block Design Test
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, adverse events assessed after 8 weeks (see notes)
Inclusion period	Not reported
Country of origin	Japan
Notes	• The primary publication (full paper article) does not describe quality of life, but an earlier published abstract, reporting the same trial, states that the investigators assessed quality of life "quantitatively according to the reported criteria" without information about the specific method. The abstract reports that participants randomised to lactulose had improved quality of life (general fatigue and abdominal distension) although no quantitative data are provided. • The investigators diagnosed 39 participants as neuropsychiatrically unimpaired and 36 participants as having minimal hepatic encephalopathy on the basis of psychometric testing. We combined the outcomes for the 2 groups in our primary analysis.

Watanabe 1997 *(Continued)*

- The investigators followed 62 of the 75 participants for 6 months after the trial and registered that 18 participants with minimal hepatic encephalopathy and 11 participants diagnosed as unimpaired continued lactulose. 5 participants with minimal hepatic encephalopathy and 4 participants who were unimpaired started de novo lactulose after completing the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. No blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants with missing outcome data are excluded from the analyses. The authors do not include information about the allocation group for participants with missing outcomes.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Wen 2013

Methods	Open, parallel-arm, single-centre, inpatient trial

Wen 2013 *(Continued)*

Participants	The trial includes 130 participants with cirrhosis experiencing an acute upper gastrointestinal haemorrhage. None had overt or minimal hepatic encephalopathy at inclusion. The trial evaluates prevention of hepatic encephalopathy. Age (mean ± SD) • Lactulose group 53.0 ± 13.3 years • Control group 50,4 ± 10.2 years Proportion of men • Lactulose group 48.4% • Control group 51.5% Aetiology of cirrhosis • Alcohol 8% • Hepatitis B/C 75%
Interventions	Lactulose syrup versus no intervention for 7 days
Outcomes	**Neuropsychiatric assessment** • Mental state (West Haven Criteria) • Number Connection Test
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, and adverse events assessed after 7 days
Inclusion period	May 2007 to July 2011
Country of origin	China
Notes	• The proportion of participants with Child's B/C was 39.7% in the lactulose group and 49.2% in the control group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Open trial. Blinding of outcome assessment.

Wen 2013 *(Continued)*

Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	The investigators account for all participants randomised. There are no missing clinical outcomes, but the trial authors exclude 2 participants who were intolerant to lactulose from the reported analyses.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Xing 2003

Methods	Open, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 45 participants with cirrhosis and minimal hepatic encephalopathy. Age (mean ± SD) • Lactulose group 33.6 ± 9.6 years • Control group 38.5 ± 6.8 years Proportion of men • Lactulose group 66.7% • Control group 58.3% Aetiology of cirrhosis • Alcohol 20.0% • Hepatitis B/C 68.9%
Interventions	Lactulose syrup versus no intervention for 4 weeks
Outcomes	**Neuropsychiatric assessment** • Number Connection Test • Verbal and Performance Intelligence Quotient tests • Blood ammonia • Electroencephalogram
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, and adverse events assessed after 4 weeks
Inclusion period	February 2000 to March 2002

Xing 2003 *(Continued)*

Country of origin	China
Notes	• Published in Chinese. • The method used to diagnose minimal hepatic encephalopathy is not described. • Participants in the intervention and control group also received vitamin B and silymarin. • Of the 48 participants randomised, 3 (1 assigned to lactulose and 2 to no intervention) did not complete the trial according to the protocol. The outcome of these participants is described in the publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. No blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised and used sufficient methods to handle missing data. Missing outcome data are unlikely to affect the analyses or to be associated with the outcome.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Yao 2014

Methods	Open, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 40 participants with cirrhosis and minimal hepatic encephalopathy. Age (mean ± SD) • Lactulose group 45.52 ± 6.34 years • Control group 45.23 ± 7.46 years Proportion of men • Lactulose and control group 67.5% Aetiology of cirrhosis • Alcohol not described • Hepatitis not described
Interventions	Lactulose syrup versus no intervention for 4 weeks
Outcomes	**Neuropsychiatric assessment** • Number Connection Test • Digit Symbol Test • Mini Mental State Examination
Outcomes included in meta-analyses	Mortality and Number Connection Test results assessed after 15 days
Inclusion period	May 2011 to July 2013
Country of origin	China
Notes	The trial report describes the effects on lactulose using surrogate outcomes and does not include information about the number of participants with (or without) an overall improvement of hepatic encephalopathy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	The authors specify that allocation was concealed, but do no specify the method of concealment.
Blinding of participants and personnel (performance bias) Non-mortality outcomes	Unclear risk	Open trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias)	Unclear risk	Open trial. No blinding of outcome assessment.

Yao 2014 *(Continued)*

Non-mortality outcomes		
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants are described and there are no missing outcome data.
Selective reporting (reporting bias)	Low risk	Predefined outcomes are reported (see notes).
For-profit funding	Unclear risk	Funding not described
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk of bias
Overall assessment (non-mortality outcomes)	High risk	High risk of bias

Zeng 2003

Methods	Open, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 60 participants with cirrhosis and minimal hepatic encephalopathy with no previous history of overt hepatic encephalopathy. Age (mean ± SD) • Short –term lactulose 50 ± 16 years • Long-term lactulose 49 ± 17 years • Control 49 ± 13 years Proportion of men • All groups 85% Aetiology of cirrhosis • Alcohol 17% • Hepatitis B/C 63%
Interventions	Lactulose syrup versus no intervention for eight or 24 weeks (see notes)
Outcomes	**Neuropsychiatric assessment** • Number Connection Test • Digit Symbol Test • Electroencephalography • Venous blood ammonia • Sensory Evoked Potentials

Zeng 2003 *(Continued)*

Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, adverse events assessed after a maximum of 24 weeks (see notes)
Inclusion period	July 1998 to March 2002
Country of origin	China
Notes	• The investigators assess quality of life using the World Health Organization quality of life BREF (WHO-QOL-BREF) including the domains physical health, psychological health, social relationships, and environment. • The method for diagnosing minimal hepatic encephalopathy is not specified. • The trial includes the following 3 allocation arms: lactulose for 8 weeks, lactulose for 24 weeks, and no intervention. We combined the results of the 2 lactulose arms in our analyses. • All participants in the intervention and control groups also received vitamin B and silymarin. • The proportion of participants with Child's B/C cirrhosis was 75% in the short–term lactulose arm, 60% in the long-term lactulose arm, and 60% in the control arm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	High risk	Open trial. No blinding of the outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	The investigators account for all participants randomised and used sufficient methods to handle missing data. Missing outcome data are unlikely to affect the analyses or to be associated with the outcome.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases

Zeng 2003 *(Continued)*

Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

Ziada 2013

Methods	Single-blind, parallel-arm, single-centre, outpatient trial
Participants	The trial includes 60 participants with cirrhosis and minimal hepatic encephalopathy. Age (mean ± SD) • Lactulose group 48.8 ± 8.2 years • Control group 51.2 ± 7.5 years Proportion of men • Lactulose group 75.0% • Control group 72.0% Aetiology of cirrhosis • Not reported
Interventions	Lactulose syrup versus no intervention for 4 weeks
Outcomes	**Neuropsychiatric assessment** • Mental status (West-Haven Criteria) • Number Connection Test A • Block Design Test • Digit Symbol Test • Serial-dotting test • Line tracing test • Blood ammonia • Cerebral magnetic resonance spectroscopy
Outcomes included in meta-analyses	Mortality, hepatic encephalopathy, and adverse events assessed after 4 weeks
Inclusion period	March 2010 to January 2012
Country of origin	Egypt
Notes	• The trial includes 90 participants randomised to lactulose (n = 30), a probiotic (n = 30), or to no treatment (n = 30). We did not include the probiotics group in our analyses. • The investigators based the diagnosis of minimal hepatic encephalopathy on the finding of at least 2 abnormal psychometric tests. • The proportion of participants with Child's B/C cirrhosis was 91.7% in the lactulose group and 88.0% in the control group.
Risk of bias	

Ziada 2013 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) Non-mortality outcomes	High risk	Open, single-blind trial. No blinding of participants or personnel.
Blinding of participants and personnel (performance bias) Mortality	Low risk	Performance bias unlikely to influence the outcome
Blinding of outcome assessment (detection bias) Non-mortality outcomes	Low risk	Open, single-blind trial. Blinding of outcome assessment.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Detection bias unlikely to influence the outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants with missing outcomes are excluded from the analyses.
Selective reporting (reporting bias)	Low risk	Predefined outcomes reported
For-profit funding	Low risk	No for-profit funding
Other bias	Low risk	No other biases
Overall assessment (mortality)	High risk	High risk
Overall assessment (non-mortality outcomes)	High risk	High risk

RCT: randomised clinical trial
SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bajaj 2010a	Observational study. Retrospective review of participants with cirrhosis maintained on lactulose following an index episode of hepatic encephalopathy. The outcomes included recurrence of hepatic encephalopathy, precipitating factors, and compliance with lactulose treatment. The analyses compared participants with/without a recurrence of hepatic encephalopathy and identified the predictors of recurrence.

Study	Reason for exclusion
Bircher 1971	Case series reporting the effects of protein intake, lactulose, and neomycin on clinical grading, electroencephalography, and blood ammonia levels in 6 participants with cirrhosis and chronic hepatic encephalopathy.
Brown 1970	Case series reporting neuropsychiatric status and associated variables in 4 participants with cirrhosis and post-shunt hepatic encephalopathy during alternating periods of treatment with lactulose and sorbitol.
James 1971	Observational study. Careful documentation of the effects of treatment with lactulose over 10 days on cerebral blood flow and metabolism in 6 participants with cirrhosis and chronic hepatic encephalopathy.
Lanthier 1985	Observational cross-over study comparing the effects of 3 months of treatment with lactulose and lactitol on mental status, psychometric performance, venous blood ammonia levels, electroencephalography mean cycle frequency, and cerebral blood flow and metabolism in 5 participants with chronic hepatic encephalopathy.
Merli 1992	Observational study on the effects of treatment with lactulose or lactitol on faecal fat excretion in 18 participants with cirrhosis.
Patil 1987	Observational study detailing the differential effects of lactulose and lactitol on (i) an in vitro faecal incubation system and (ii) on terminal ileal and colonic pH in 6 normal participants using radiotelemetry.
Piotraschke 1996	Observational open study published in abstract form describing the non-comparative effect of lactulose on preventing hepatic encephalopathy in participants with cirrhosis following insertion of a transjugular intrahepatic portosystemic shunt.
Pockros 2009	Randomised clinical trial of lactulose versus AST-120 (spherical carbon adsorbent). The trial includes 47 participants with cirrhosis and overt hepatic encephalopathy. The trial did not include a placebo or no intervention group.
Quinton 1982	Randomised clinical trial of mannitol lavage versus a combination of lactulose and the antibiotic kanamycin for the prevention of hepatic encephalopathy following gastrointestinal haemorrhage in participants with cirrhosis. The trial did not include a placebo/no intervention group.
Rahimi 2014	Randomised clinical trial on lactulose versus polyethylene glycol for the treatment of acute hepatic encephalopathy. The trial did not include a placebo/no intervention group.
Riggio 1990	Observational study comparing the effect of lactulose or lactitol on the faecal flora of 21 participants with cirrhosis and no evidence of hepatic encephalopathy.
Rorsman 1970	Case series reporting the responses of 3 participants with cirrhosis and post-shunt hepatic encephalopathy to treatment with lactulose.
Salerno 1994	Observational study on the differential effects of 2 different doses of lactitol on neuropsychiatric status in participants with cirrhosis.
Schomerus 1993	A field study documenting the prevalence of minimal hepatic encephalopathy in ambulatory participants with cirrhosis.
Sharma 2008	Randomised trial of lactulose versus probiotics for the treatment of minimal hepatic encephalopathy. The trial does not include a placebo or no intervention group.
Sharma 2009a	Observational study to identify the predictors of minimal hepatic encephalopathy in participants with cirrhosis.

Study	Reason for exclusion
Sharma 2010	Observational study evaluating predictors of non-response to lactulose in participants with cirrhosis and overt hepatic encephalopathy.
Sharma 2010a	Observational study evaluating the prevalence of abnormal psychometric tests and critical flicker frequency after clinical recovery of overt hepatic encephalopathy.
Sharma 2011a	Retrospective review of the efficacy of lactulose for the treatment of hepatic encephalopathy in young people with hepatic encephalopathy.
Trovato 1995	Observational study of the effects of lactitol on clinical status and blood ammonium, atrial natriuretic peptide, and amino acid concentrations in 10 participants with cirrhosis and hepatic encephalopathy.
Vendemiale 1992	An open comparison of the effects of 10 days treatment with lactulose or no treatment on blood ammonia levels, Number Connection Test results, and lymphocyte sub-populations in people with cirrhosis.
Venturini 2005	Randomised clinical trial of the effect of rifaximin, lactulose, and placebo on circulating benzodiazepine-like compounds in 18 participants with cirrhosis. None of the included participants had hepatic encephalopathy.
Zeegen 1970	Case series describes the effects of treatment with lactulose in 5 participants with cirrhosis and overt hepatic encephalopathy.

Characteristics of ongoing studies *[ordered by study ID]*

Salih 2007

Trial name or title	Lactulose for the prevention of hepatic encephalopathy in participants with cirrhosis and upper gastrointestinal haemorrhage
Methods	Randomised clinical trial
Participants	Participants with cirrhosis
Interventions	Lactulose versus placebo
Outcomes	Hepatic encephalopathy
Starting date	2007
Contact information	Aga Kahn University
Trial registration number	NCT00553423
Notes	Investigators contacted via email October 2014. No reply

Wang 2012

Trial name or title	Impact of lactulose treatment on cognition, assessment of quality of life and changes of intestinal flora in minimal hepatic encephalopathy participants: a multicentre, randomised, open-label and controlled clinical study

Wang 2012 *(Continued)*

Methods	Randomised clinical trial
Participants	Cirrhosis and minimal hepatic encephalopathy
Interventions	Lactulose versus no intervention
Outcomes	Recovery from minimal hepatic encephalopathy
Starting date	2012
Contact information	Zhong Shan Hospital, Shanghai, China
Trial registration number	ChiCTR-TRC-12002342
Notes	Investigators contacted via email October 2014 and reported that the final analyses will take place in October 2014

DATA AND ANALYSES

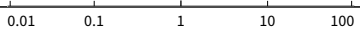
Comparison 1. Non-absorbable disaccharides versus placebo/no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	24	1487	Risk Ratio (IV, Random, 95% CI)	0.59 [0.40, 0.87]
2 Mortality in trials with a low risk of bias	8	705	Risk Ratio (IV, Random, 95% CI)	0.63 [0.41, 0.97]
3 Hepatic encephalopathy	22	1415	Risk Ratio (IV, Random, 95% CI)	0.58 [0.50, 0.69]
4 Serious adverse events	24	1487	Risk Ratio (IV, Random, 95% CI)	0.47 [0.36, 0.60]
5 Quality of life: sickness impact profile	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Change from baseline	2	120	Mean Difference (IV, Random, 95% CI)	7.18 [5.28, 9.07]
5.2 End of treatment	1	40	Mean Difference (IV, Random, 95% CI)	0.90 [-4.13, 5.93]
6 Non-serious adverse events	9		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.1 Overall	9	739	Risk Ratio (IV, Random, 95% CI)	2.47 [1.24, 4.93]
6.2 Diarrhoea	7	634	Risk Ratio (IV, Random, 95% CI)	6.41 [1.84, 22.40]
6.3 Bloating	6	563	Risk Ratio (IV, Random, 95% CI)	4.50 [1.17, 17.27]
6.4 Nausea	1	60	Risk Ratio (IV, Random, 95% CI)	11.00 [0.64, 190.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.5 Constipation	2	298	Risk Ratio (IV, Random, 95% CI)	0.04 [0.01, 0.29]
6.6 Hyponatraemia	1	45	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.11]
6.7 Anal fissure	1	45	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.11]
6.8 Hyperglycaemia	1	45	Risk Ratio (IV, Random, 95% CI)	0.35 [0.01, 8.11]
7 Number connection test, end of treatment	6	275	Mean Difference (IV, Random, 95% CI)	-5.56 [-11.59, 0.47]
8 Ammonia end of treatment	6	374	Mean Difference (IV, Random, 95% CI)	-11.64 [-21.14, -2.14]
8.1 Venous	5	216	Mean Difference (IV, Random, 95% CI)	-15.66 [-27.79, -3.53]
8.2 Arterial	1	158	Mean Difference (IV, Random, 95% CI)	-2.23 [-6.89, 2.43]
9 Ammonia change from baseline	3	155	Mean Difference (IV, Random, 95% CI)	18.97 [8.86, 29.09]
9.1 Arterial	2	134	Mean Difference (IV, Random, 95% CI)	10.45 [5.60, 15.31]
9.2 Venous	1	21	Mean Difference (IV, Random, 95% CI)	44.0 [32.34, 55.66]
10 Mortality in worst-case scenario analyses	24		Risk Ratio (IV, Random, 95% CI)	Subtotals only
10.1 Worst-case scenario	24	1487	Risk Ratio (IV, Random, 95% CI)	0.61 [0.42, 0.88]
10.2 Extreme worst-case scenario analysis	24	1487	Risk Ratio (IV, Random, 95% CI)	0.64 [0.44, 0.94]
11 Hepatic encephalopathy worst-case scenario analysis	22	2830	Risk Ratio (IV, Random, 95% CI)	0.60 [0.54, 0.66]
11.1 Worst-case scenario	22	1415	Risk Ratio (IV, Random, 95% CI)	0.59 [0.50, 0.69]
11.2 Extreme worst-case scenario	22	1415	Risk Ratio (IV, Random, 95% CI)	0.60 [0.51, 0.70]
12 Serious adverse events worst-case scenario analysis	24	2974	Risk Ratio (IV, Random, 95% CI)	0.48 [0.41, 0.57]
12.1 Worst-case scenario analysis	24	1487	Risk Ratio (IV, Random, 95% CI)	0.47 [0.37, 0.61]
12.2 Extreme worst-case scenario analysis	24	1487	Risk Ratio (IV, Random, 95% CI)	0.49 [0.38, 0.62]

Analysis 1.1. Comparison 1 Non-absorbable disaccharides versus placebo/no intervention, Outcome 1 Mortality.

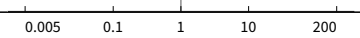
Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Agrawal 2012	13/80	16/78		33.39%	0.79[0.41,1.54]
Corazza 1982	0/16	0/16			Not estimable
Dhiman 2000	2/14	1/12		2.83%	1.71[0.18,16.65]
Germain 1973	0/9	0/9			Not estimable
Horsmans 1997	0/7	0/7			Not estimable
Jain 2013	1/30	1/30		1.97%	1[0.07,15.26]
Li 1999	0/48	0/38			Not estimable
Mittal 2011	0/40	1/40		1.46%	0.33[0.01,7.95]
Prasad 2007	0/31	3/30		1.71%	0.14[0.01,2.57]
Quero 1997	1/20	0/20		1.48%	3[0.13,69.52]
Raza 2004	1/18	2/13		2.79%	0.36[0.04,3.57]
Riggio 2005	2/25	1/25		2.68%	2[0.19,20.67]
Sharma 2009	5/70	11/70		14.52%	0.45[0.17,1.24]
Sharma 2011	3/35	6/35		8.6%	0.5[0.14,1.84]
Sharma 2012	5/60	10/60		14.29%	0.5[0.18,1.38]
Simmons 1970	3/14	6/12		11.04%	0.43[0.14,1.36]
Uribe 1987a	0/22	4/23		1.78%	0.12[0.01,2.04]
Uribe 1987b	0/10	0/10			Not estimable
Watanabe 1997	0/41	0/34			Not estimable
Wen 2013	0/65	1/65		1.45%	0.33[0.01,8.03]
Xing 2003	0/23	0/22			Not estimable
Yao 2014	0/20	0/20			Not estimable
Zeng 2003	0/40	0/20			Not estimable
Ziada 2013	0/30	0/30			Not estimable
Total (95% CI)	**768**	**719**		**100%**	**0.59[0.4,0.87]**
Total events: 36 (Disaccharide), 63 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.16, df=13(P=0.89); I^2=0%					
Test for overall effect: Z=2.7(P=0.01)					



Favours disaccharide — Favours control

Analysis 1.2. Comparison 1 Non-absorbable disaccharides versus placebo/no intervention, Outcome 2 Mortality in trials with a low risk of bias.

Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Sharma 2011	3/35	6/35		10.82%	0.5[0.14,1.84]
Dhiman 2000	2/14	1/12		3.56%	1.71[0.18,16.65]
Sharma 2012	5/60	10/60		17.97%	0.5[0.18,1.38]
Mittal 2011	0/40	1/40		1.83%	0.33[0.01,7.95]
Sharma 2009	5/70	11/70		18.27%	0.45[0.17,1.24]
Riggio 2005	2/25	1/25		3.38%	2[0.19,20.67]
Prasad 2007	0/31	3/30		2.16%	0.14[0.01,2.57]
Agrawal 2012	13/80	16/78		42.01%	0.79[0.41,1.54]
Total (95% CI)	**355**	**350**		**100%**	**0.63[0.41,0.97]**



Favours disaccharide — Favours control

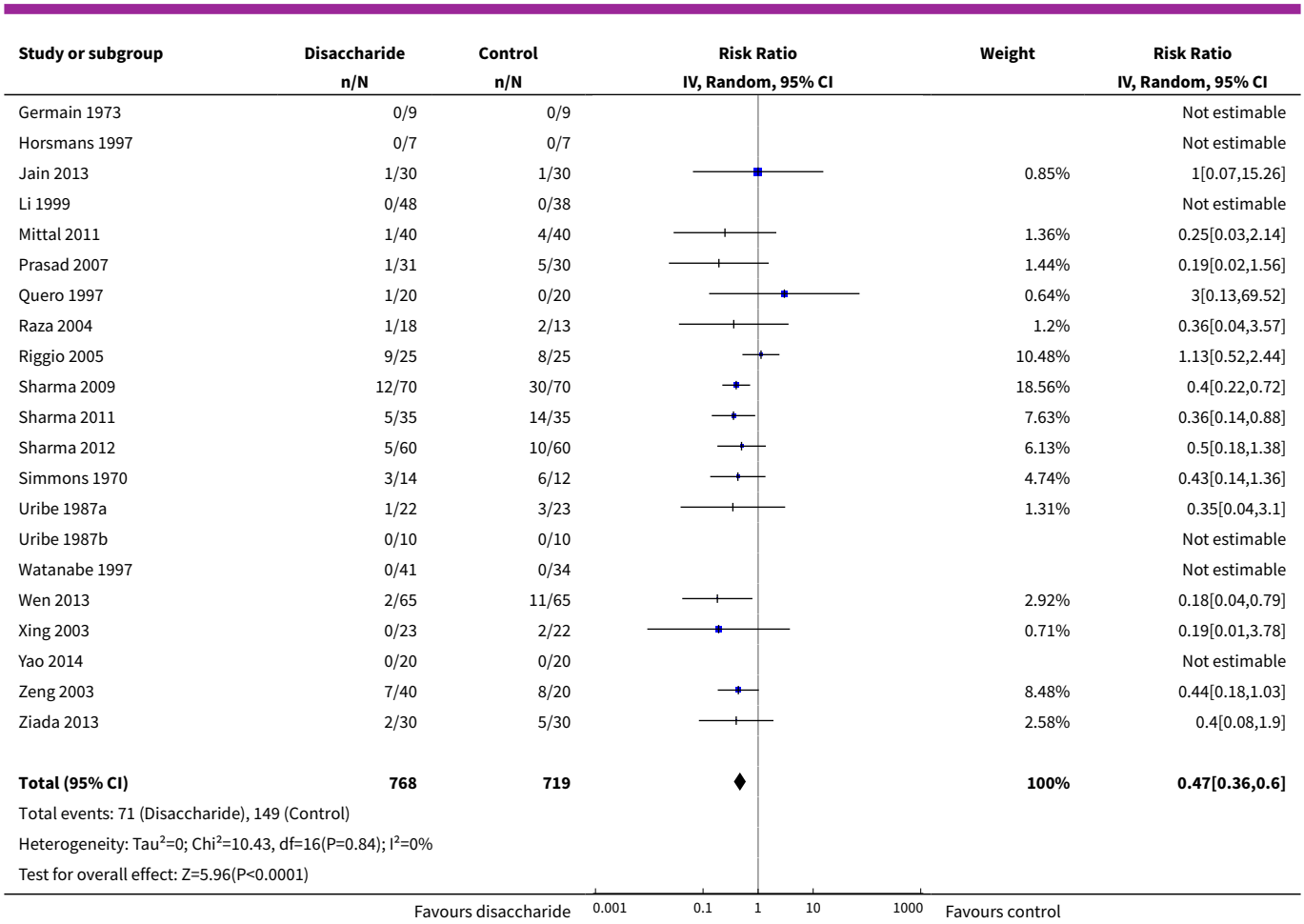
Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Total events: 30 (Disaccharide), 49 (Control)					
Heterogeneity: Tau²=0; Chi²=4.06, df=7(P=0.77); I²=0%					
Test for overall effect: Z=2.11(P=0.03)					

Analysis 1.3. Comparison 1 Non-absorbable disaccharides versus placebo/no intervention, Outcome 3 Hepatic encephalopathy.

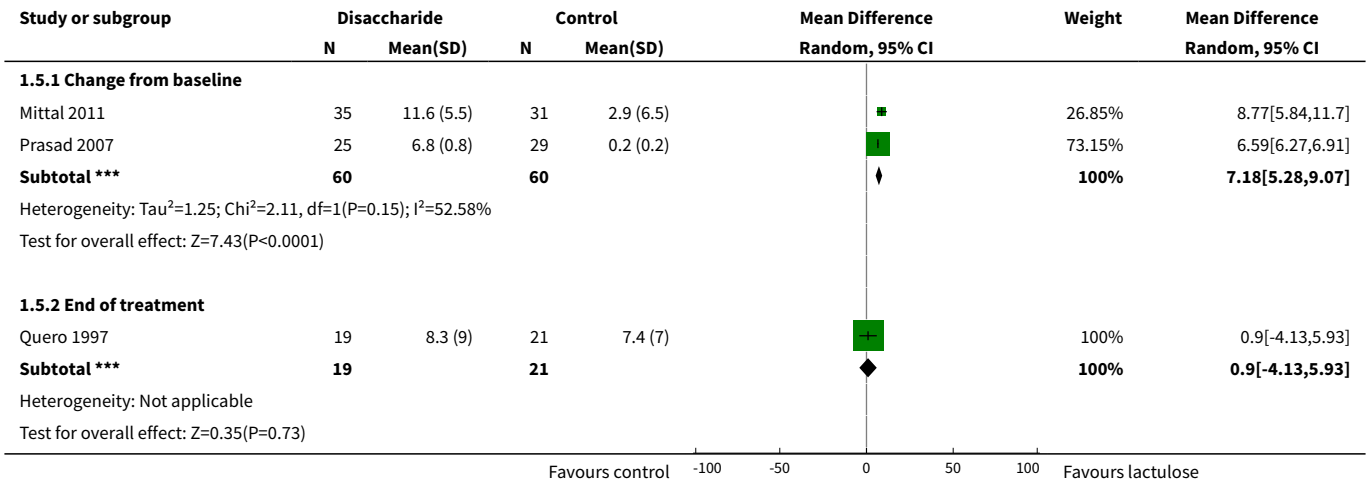
Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Agrawal 2012	18/80	37/78		7.16%	0.47[0.3,0.76]
Dhiman 2000	6/14	12/12		5.35%	0.45[0.25,0.81]
Germain 1973	4/9	3/9		1.74%	1.33[0.41,4.33]
Horsmans 1997	6/7	6/7		7.95%	1[0.65,1.53]
Jain 2013	2/30	2/30		0.72%	1[0.15,6.64]
Li 1999	22/48	28/38		9.42%	0.62[0.43,0.89]
Mittal 2011	21/40	36/40		10.66%	0.58[0.43,0.8]
Prasad 2007	6/31	20/30		3.65%	0.29[0.14,0.62]
Quero 1997	0/20	1/20		0.27%	0.33[0.01,7.72]
Raza 2004	7/18	8/13		3.97%	0.63[0.31,1.3]
Riggio 2005	9/25	8/25		3.55%	1.13[0.52,2.44]
Sharma 2009	12/70	30/70		5.44%	0.4[0.22,0.72]
Sharma 2011	5/35	14/35		2.74%	0.36[0.14,0.88]
Sharma 2012	6/60	14/60		2.85%	0.43[0.18,1.04]
Simmons 1970	4/14	5/12		2.08%	0.69[0.24,1.99]
Uribe 1987a	3/22	8/23		1.7%	0.39[0.12,1.29]
Uribe 1987b	1/10	6/10		0.69%	0.17[0.02,1.14]
Watanabe 1997	13/41	12/34		4.76%	0.9[0.47,1.7]
Wen 2013	2/65	11/65		1.16%	0.18[0.04,0.79]
Xing 2003	11/23	22/22		8.08%	0.49[0.32,0.75]
Zeng 2003	7/40	8/20		2.99%	0.44[0.18,1.03]
Ziada 2013	22/30	29/30		13.09%	0.76[0.61,0.95]
Total (95% CI)	**732**	**683**		**100%**	**0.58[0.5,0.69]**
Total events: 187 (Disaccharide), 320 (Control)					
Heterogeneity: Tau²=0.04; Chi²=30.96, df=21(P=0.07); I²=32.17%					
Test for overall effect: Z=6.44(P<0.0001)					

Analysis 1.4. Comparison 1 Non-absorbable disaccharides versus placebo/no intervention, Outcome 4 Serious adverse events.

Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Agrawal 2012	18/80	37/78		28.56%	0.47[0.3,0.76]
Corazza 1982	0/16	0/16			Not estimable
Dhiman 2000	2/14	3/12		2.41%	0.57[0.11,2.87]

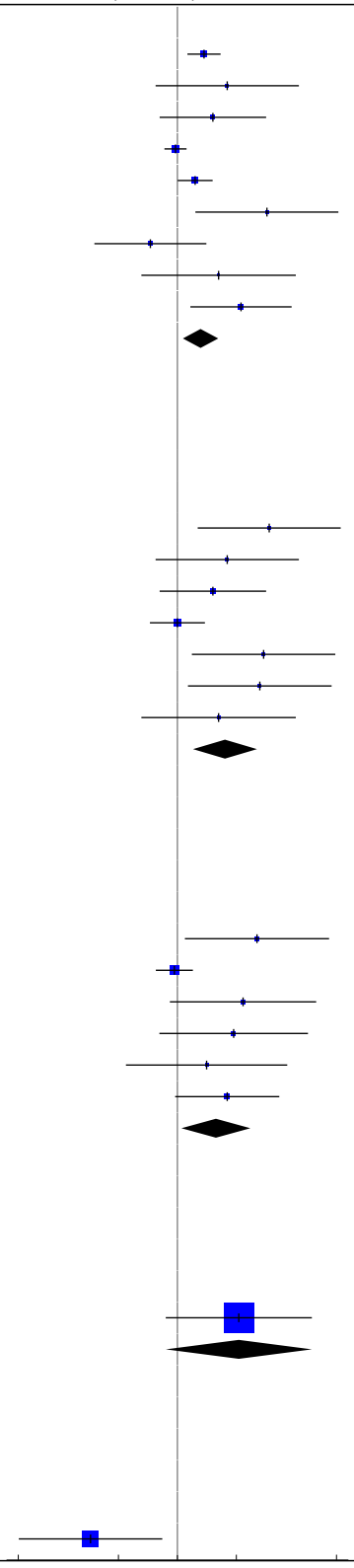


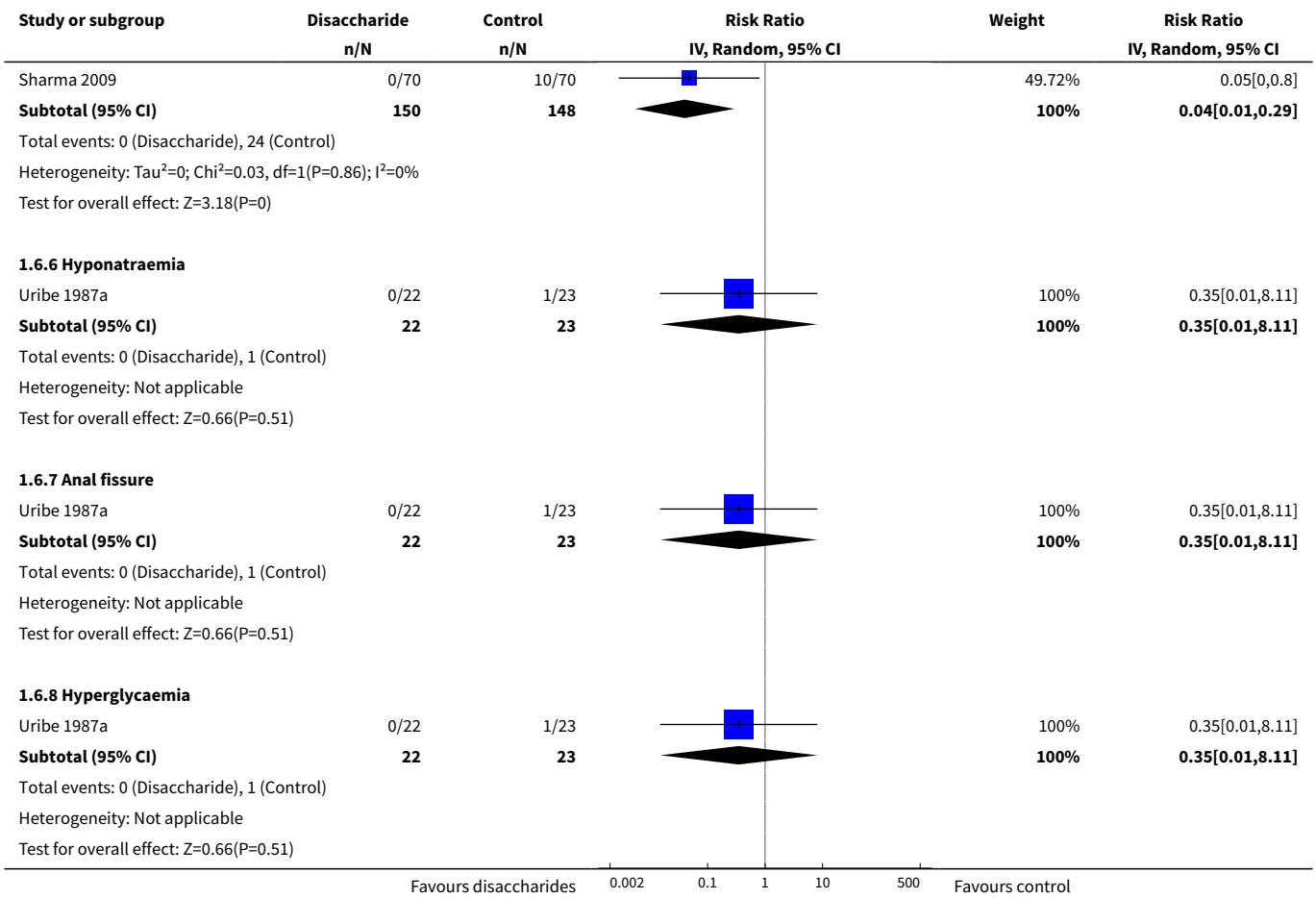
Analysis 1.5. Comparison 1 Non-absorbable disaccharides versus placebo/ no intervention, Outcome 5 Quality of life: sickness impact profile.



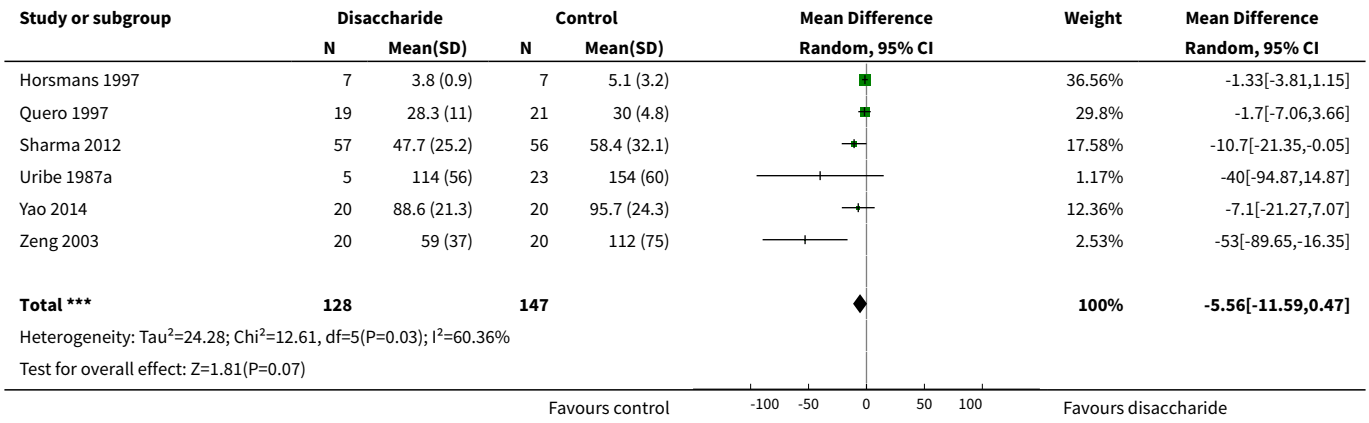
Analysis 1.6. Comparison 1 Non-absorbable disaccharides versus placebo/no intervention, Outcome 6 Non-serious adverse events.

Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.6.1 Overall					
Agrawal 2012	29/80	10/78		20.35%	2.83[1.48,5.4]
Horsmans 1997	3/7	0/7		4.9%	7[0.43,114.7]
McClain 1984	4/16	1/16		7.65%	4[0.5,31.98]
Quero 1997	13/20	14/20		22.59%	0.93[0.6,1.43]
Sharma 2009	20/70	10/70		19.95%	2[1.01,3.96]
Sharma 2012	16/60	0/60		4.92%	33[2.02,537.82]
Uribe 1987a	1/22	3/23		7.12%	0.35[0.04,3.1]
Wen 2013	2/65	0/65		4.33%	5[0.24,102.16]
Ziada 2013	12/30	1/30		8.19%	12[1.66,86.59]
Subtotal (95% CI)	**370**	**369**		**100%**	**2.47[1.24,4.93]**
Total events: 100 (Disaccharide), 39 (Control)					
Heterogeneity: Tau^2=0.5; Chi^2=22.24, df=8(P=0); I^2=64.04%					
Test for overall effect: Z=2.56(P=0.01)					
1.6.2 Diarrhoea					
Agrawal 2012	18/80	0/78		12.04%	36.09[2.21,588.62]
Horsmans 1997	3/7	0/7		12.01%	7[0.43,114.7]
McClain 1984	4/16	1/16		16.43%	4[0.5,31.98]
Quero 1997	5/20	5/20		24.62%	1[0.34,2.93]
Sharma 2009	14/70	0/70		12%	29[1.76,476.86]
Sharma 2012	12/60	0/60		11.97%	25[1.51,412.9]
Wen 2013	2/65	0/65		10.94%	5[0.24,102.16]
Subtotal (95% CI)	**318**	**316**		**100%**	**6.41[1.84,22.4]**
Total events: 58 (Disaccharide), 6 (Control)					
Heterogeneity: Tau^2=1.35; Chi^2=12.27, df=6(P=0.06); I^2=51.11%					
Test for overall effect: Z=2.91(P=0)					
1.6.3 Bloating					
Agrawal 2012	11/80	0/78		13.45%	22.43[1.34,374.24]
Quero 1997	8/20	9/20		29.93%	0.89[0.43,1.83]
Sharma 2009	6/70	0/70		13.21%	13[0.75,226.45]
Sharma 2012	4/60	0/60		12.98%	9[0.5,163.58]
Uribe 1987a	1/22	0/23		11.71%	3.13[0.13,72.99]
Ziada 2013	7/30	1/30		18.73%	7[0.92,53.47]
Subtotal (95% CI)	**282**	**281**		**100%**	**4.5[1.17,17.27]**
Total events: 37 (Disaccharide), 10 (Control)					
Heterogeneity: Tau^2=1.44; Chi^2=11.53, df=5(P=0.04); I^2=56.64%					
Test for overall effect: Z=2.19(P=0.03)					
1.6.4 Nausea					
Ziada 2013	5/30	0/30		100%	11[0.64,190.53]
Subtotal (95% CI)	**30**	**30**		**100%**	**11[0.64,190.53]**
Total events: 5 (Disaccharide), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.65(P=0.1)					
1.6.5 Constipation					
Agrawal 2012	0/80	14/78		50.28%	0.03[0,0.55]





Analysis 1.7. Comparison 1 Non-absorbable disaccharides versus placebo/ no intervention, Outcome 7 Number connection test, end of treatment.



Analysis 1.8. Comparison 1 Non-absorbable disaccharides versus placebo/no intervention, Outcome 8 Ammonia end of treatment.

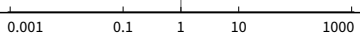
Study or subgroup	Disaccharide N	Disaccharide Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.8.1 Venous							
Corazza 1982	16	62.1 (9)	16	77.3 (6.1)		25.84%	-15.19[-20.52,-9.86]
Riggio 2005	25	125 (12.7)	25	126.4 (17.8)		22.89%	-1.4[-9.97,7.17]
Uribe 1987a	22	146 (54)	23	170 (73)		5.24%	-24[-61.41,13.41]
Zeng 2003	20	121 (61)	20	208 (110)		2.69%	-87[-142.13,-31.87]
Ziada 2013	24	55.6 (28.1)	25	74.5 (23.3)		17%	-18.9[-33.39,-4.41]
Subtotal ***	**107**		**109**			**73.66%**	**-15.66[-27.79,-3.53]**
Heterogeneity: Tau^2=106.89; Chi^2=15.55, df=4(P=0); I^2=74.27%							
Test for overall effect: Z=2.53(P=0.01)							
1.8.2 Arterial							
Agrawal 2012	80	83 (12.9)	78	85.2 (16.7)		26.34%	-2.23[-6.89,2.43]
Subtotal ***	**80**		**78**			**26.34%**	**-2.23[-6.89,2.43]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.94(P=0.35)							
Total ***	**187**		**187**			**100%**	**-11.64[-21.14,-2.14]**
Heterogeneity: Tau^2=83.49; Chi^2=25.92, df=5(P<0.0001); I^2=80.71%							
Test for overall effect: Z=2.4(P=0.02)							
Test for subgroup differences: Chi^2=4.1, df=1 (P=0.04), I^2=75.62%							

Analysis 1.9. Comparison 1 Non-absorbable disaccharides versus placebo/no intervention, Outcome 9 Ammonia change from baseline.

Study or subgroup	Disaccharide N	Disaccharide Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.9.1 Arterial							
Jain 2013	27	26 (7)	27	13.1 (2.8)		37.35%	12.9[10.08,15.72]
Mittal 2011	40	8.5 (5.8)	40	0.5 (7.8)		37.2%	7.95[4.94,10.96]
Subtotal ***	**67**		**67**			**74.55%**	**10.45[5.6,15.31]**
Heterogeneity: Tau^2=10.04; Chi^2=5.53, df=1(P=0.02); I^2=81.92%							
Test for overall effect: Z=4.22(P<0.0001)							
1.9.2 Venous							
Simmons 1970	11	55 (6.7)	10	11 (17.7)		25.45%	44[32.34,55.66]
Subtotal ***	**11**		**10**			**25.45%**	**44[32.34,55.66]**
Heterogeneity: Not applicable							
Test for overall effect: Z=7.39(P<0.0001)							
Total ***	**78**		**77**			**100%**	**18.97[8.86,29.09]**
Heterogeneity: Tau^2=69.24; Chi^2=36.1, df=2(P<0.0001); I^2=94.46%							
Test for overall effect: Z=3.68(P=0)							
Test for subgroup differences: Chi^2=27.09, df=1 (P<0.0001), I^2=96.31%							

Analysis 1.10. Comparison 1 Non-absorbable disaccharides versus placebo/no intervention, Outcome 10 Mortality in worst-case scenario analyses.

Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.10.1 Worst-case scenario					
Agrawal 2012	13/80	16/78		30.59%	0.79[0.41,1.54]
Corazza 1982	0/16	0/16			Not estimable
Dhiman 2000	2/14	1/12		2.59%	1.71[0.18,16.65]
Germain 1973	0/9	0/9			Not estimable
Horsmans 1997	0/7	0/7			Not estimable
Jain 2013	1/30	1/30		1.81%	1[0.07,15.26]
Li 1999	0/48	0/38			Not estimable
Mittal 2011	0/40	1/40		1.33%	0.33[0.01,7.95]
Prasad 2007	0/31	3/30		1.57%	0.14[0.01,2.57]
Quero 1997	1/20	0/20		1.36%	3[0.13,69.52]
Raza 2004	2/18	3/13		4.98%	0.48[0.09,2.48]
Riggio 2005	2/25	1/25		2.46%	2[0.19,20.67]
Sharma 2009	5/70	11/70		13.3%	0.45[0.17,1.24]
Sharma 2011	3/35	6/35		7.88%	0.5[0.14,1.84]
Sharma 2012	5/60	10/60		13.09%	0.5[0.18,1.38]
Simmons 1970	3/14	6/12		10.11%	0.43[0.14,1.36]
Uribe 1987a	0/22	4/23		1.63%	0.12[0.01,2.04]
Uribe 1987b	0/10	0/10			Not estimable
Watanabe 1997	0/41	0/34			Not estimable
Wen 2013	3/65	3/65		5.49%	1[0.21,4.77]
Xing 2003	0/23	0/22			Not estimable
Yao 2014	0/20	0/20			Not estimable
Zeng 2003	1/40	1/20		1.81%	0.5[0.03,7.59]
Ziada 2013	0/30	0/30			Not estimable
Subtotal (95% CI)	**768**	**719**		**100%**	**0.61[0.42,0.88]**
Total events: 41 (Disaccharide), 67 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.33, df=14(P=0.92); I^2=0%					
Test for overall effect: Z=2.63(P=0.01)					
1.10.2 Extreme worst-case scenario analysis					
Agrawal 2012	13/80	16/78		31.94%	0.79[0.41,1.54]
Corazza 1982	0/16	0/16			Not estimable
Dhiman 2000	2/14	1/12		2.71%	1.71[0.18,16.65]
Germain 1973	0/9	0/9			Not estimable
Horsmans 1997	0/7	0/7			Not estimable
Jain 2013	1/30	1/30		1.88%	1[0.07,15.26]
Li 1999	0/48	0/38			Not estimable
Mittal 2011	0/40	1/40		1.39%	0.33[0.01,7.95]
Prasad 2007	0/31	3/30		1.64%	0.14[0.01,2.57]
Quero 1997	1/20	0/20		1.42%	3[0.13,69.52]
Raza 2004	2/18	2/13		4.2%	0.72[0.12,4.48]
Riggio 2005	2/25	1/25		2.57%	2[0.19,20.67]
Sharma 2009	5/70	11/70		13.89%	0.45[0.17,1.24]
Sharma 2011	3/35	6/35		8.23%	0.5[0.14,1.84]
Sharma 2012	5/60	10/60		13.67%	0.5[0.18,1.38]
Simmons 1970	3/14	6/12		10.56%	0.43[0.14,1.36]
Uribe 1987a	0/22	4/23		1.71%	0.12[0.01,2.04]
Uribe 1987b	0/10	0/10			Not estimable



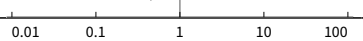
Favours disaccharide — Favours control

Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Watanabe 1997	0/41	0/34			Not estimable
Wen 2013	3/65	1/65		2.8%	3[0.32,28.09]
Xing 2003	0/23	0/22			Not estimable
Yao 2014	0/20	0/20			Not estimable
Zeng 2003	1/40	0/20		1.4%	1.54[0.07,36.11]
Ziada 2013	0/30	0/30			Not estimable
Subtotal (95% CI)	**768**	**719**		**100%**	**0.64[0.44,0.94]**
Total events: 41 (Disaccharide), 63 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.07, df=14(P=0.83); I^2=0%					
Test for overall effect: Z=2.3(P=0.02)					
Test for subgroup differences: Chi^2=0.04, df=1 (P=0.84), I^2=0%					

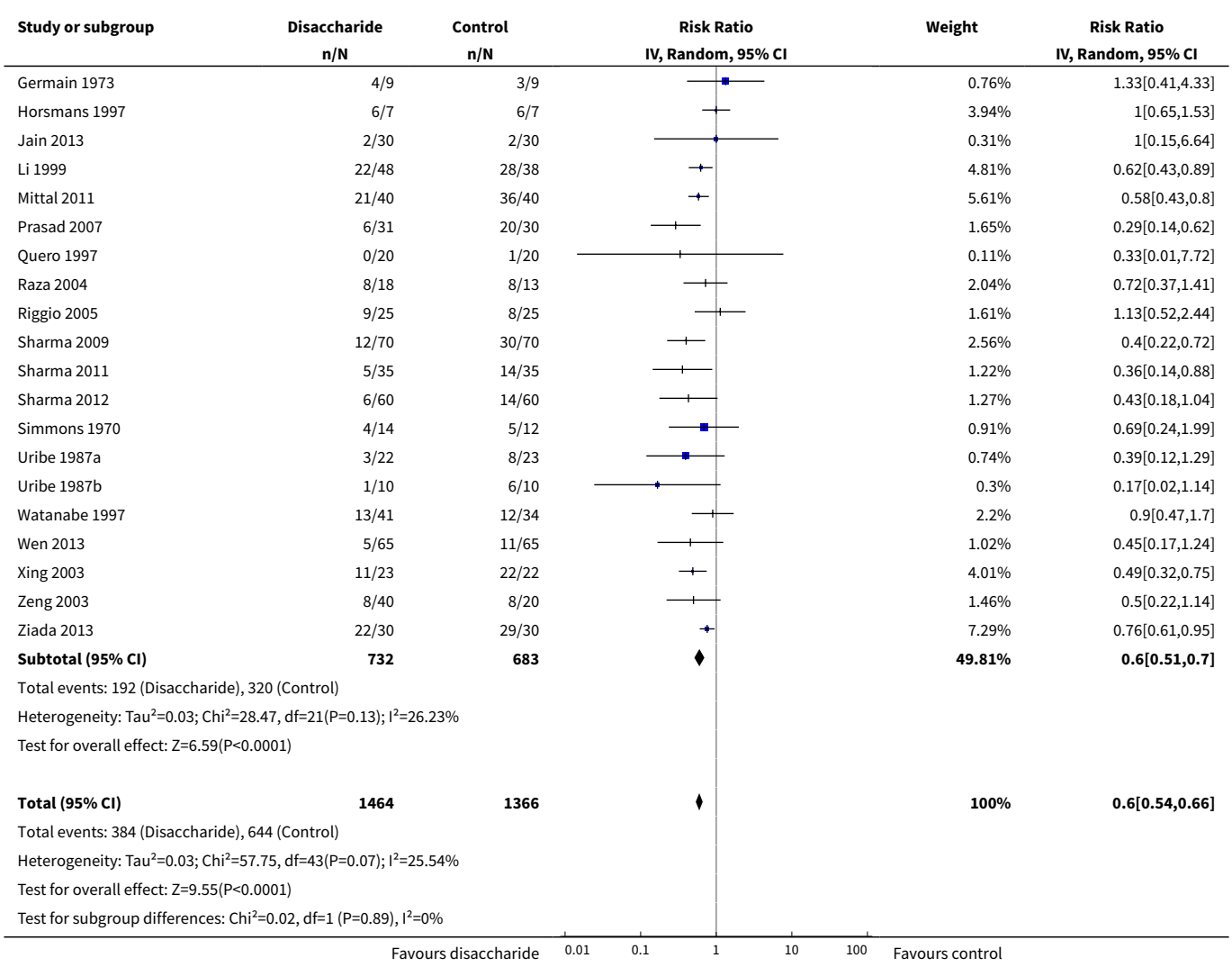
Favours disaccharide — Favours control

Analysis 1.11. Comparison 1 Non-absorbable disaccharides versus placebo/no intervention, Outcome 11 Hepatic encephalopathy worst-case scenario analysis.

Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.11.1 Worst-case scenario					
Agrawal 2012	18/80	37/78		3.49%	0.47[0.3,0.76]
Dhiman 2000	6/14	12/12		2.51%	0.45[0.25,0.81]
Germain 1973	4/9	3/9		0.76%	1.33[0.41,4.33]
Horsmans 1997	6/7	6/7		3.94%	1[0.65,1.53]
Jain 2013	2/30	2/30		0.31%	1[0.15,6.64]
Li 1999	22/48	28/38		4.81%	0.62[0.43,0.89]
Mittal 2011	21/40	36/40		5.61%	0.58[0.43,0.8]
Prasad 2007	6/31	20/30		1.65%	0.29[0.14,0.62]
Quero 1997	0/20	1/20		0.11%	0.33[0.01,7.72]
Raza 2004	8/18	9/13		2.25%	0.64[0.34,1.21]
Riggio 2005	9/25	8/25		1.61%	1.13[0.52,2.44]
Sharma 2009	12/70	30/70		2.56%	0.4[0.22,0.72]
Sharma 2011	5/35	14/35		1.22%	0.36[0.14,0.88]
Sharma 2012	6/60	14/60		1.27%	0.43[0.18,1.04]
Simmons 1970	4/14	5/12		0.91%	0.69[0.24,1.99]
Uribe 1987a	3/22	8/23		0.74%	0.39[0.12,1.29]
Uribe 1987b	1/10	6/10		0.3%	0.17[0.02,1.14]
Watanabe 1997	13/41	12/34		2.2%	0.9[0.47,1.7]
Wen 2013	5/65	13/65		1.08%	0.38[0.15,1.02]
Xing 2003	11/23	22/22		4.01%	0.49[0.32,0.75]
Zeng 2003	8/40	9/20		1.56%	0.44[0.2,0.98]
Ziada 2013	22/30	29/30		7.29%	0.76[0.61,0.95]
Subtotal (95% CI)	**732**	**683**		**50.19%**	**0.59[0.5,0.69]**
Total events: 192 (Disaccharide), 324 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=29.27, df=21(P=0.11); I^2=28.25%					
Test for overall effect: Z=6.68(P<0.0001)					
1.11.2 Extreme worst-case scenario					
Agrawal 2012	18/80	37/78		3.49%	0.47[0.3,0.76]
Dhiman 2000	6/14	12/12		2.51%	0.45[0.25,0.81]

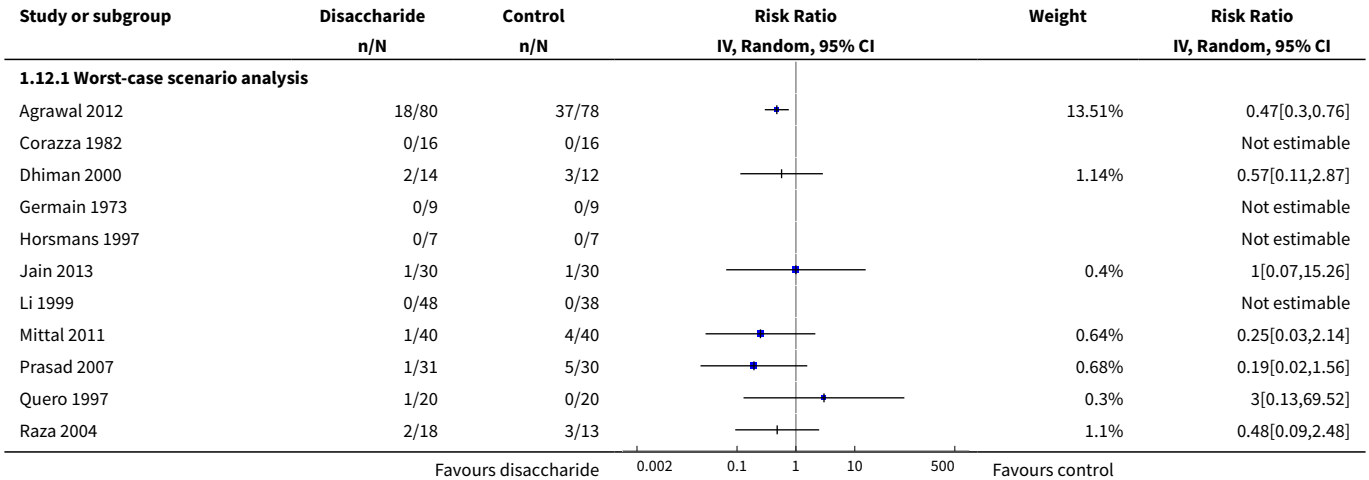


Favours disaccharide — Favours control



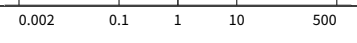
Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Germain 1973	4/9	3/9		0.76%	1.33[0.41,4.33]
Horsmans 1997	6/7	6/7		3.94%	1[0.65,1.53]
Jain 2013	2/30	2/30		0.31%	1[0.15,6.64]
Li 1999	22/48	28/38		4.81%	0.62[0.43,0.89]
Mittal 2011	21/40	36/40		5.61%	0.58[0.43,0.8]
Prasad 2007	6/31	20/30		1.65%	0.29[0.14,0.62]
Quero 1997	0/20	1/20		0.11%	0.33[0.01,7.72]
Raza 2004	8/18	8/13		2.04%	0.72[0.37,1.41]
Riggio 2005	9/25	8/25		1.61%	1.13[0.52,2.44]
Sharma 2009	12/70	30/70		2.56%	0.4[0.22,0.72]
Sharma 2011	5/35	14/35		1.22%	0.36[0.14,0.88]
Sharma 2012	6/60	14/60		1.27%	0.43[0.18,1.04]
Simmons 1970	4/14	5/12		0.91%	0.69[0.24,1.99]
Uribe 1987a	3/22	8/23		0.74%	0.39[0.12,1.29]
Uribe 1987b	1/10	6/10		0.3%	0.17[0.02,1.14]
Watanabe 1997	13/41	12/34		2.2%	0.9[0.47,1.7]
Wen 2013	5/65	11/65		1.02%	0.45[0.17,1.24]
Xing 2003	11/23	22/22		4.01%	0.49[0.32,0.75]
Zeng 2003	8/40	8/20		1.46%	0.5[0.22,1.14]
Ziada 2013	22/30	29/30		7.29%	0.76[0.61,0.95]
Subtotal (95% CI)	**732**	**683**		**49.81%**	**0.6[0.51,0.7]**
Total events: 192 (Disaccharide), 320 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=28.47, df=21(P=0.13); I^2=26.23%					
Test for overall effect: Z=6.59(P<0.0001)					
Total (95% CI)	**1464**	**1366**		**100%**	**0.6[0.54,0.66]**
Total events: 384 (Disaccharide), 644 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=57.75, df=43(P=0.07); I^2=25.54%					
Test for overall effect: Z=9.55(P<0.0001)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.89), I^2=0%					

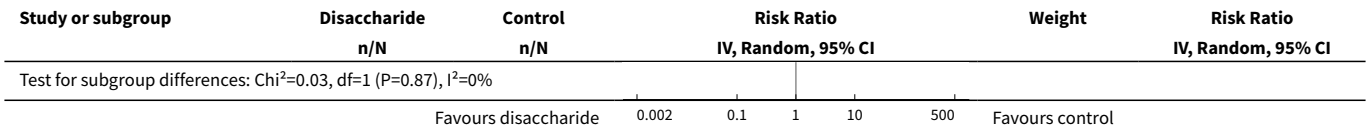
Analysis 1.12. Comparison 1 Non-absorbable disaccharides versus placebo/ no intervention, Outcome 12 Serious adverse events worst-case scenario analysis.



Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.12.1 Worst-case scenario analysis					
Agrawal 2012	18/80	37/78		13.51%	0.47[0.3,0.76]
Corazza 1982	0/16	0/16			Not estimable
Dhiman 2000	2/14	3/12		1.14%	0.57[0.11,2.87]
Germain 1973	0/9	0/9			Not estimable
Horsmans 1997	0/7	0/7			Not estimable
Jain 2013	1/30	1/30		0.4%	1[0.07,15.26]
Li 1999	0/48	0/38			Not estimable
Mittal 2011	1/40	4/40		0.64%	0.25[0.03,2.14]
Prasad 2007	1/31	5/30		0.68%	0.19[0.02,1.56]
Quero 1997	1/20	0/20		0.3%	3[0.13,69.52]
Raza 2004	2/18	3/13		1.1%	0.48[0.09,2.48]

Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Riggio 2005	9/25	8/25		4.95%	1.13[0.52,2.44]
Sharma 2009	12/70	30/70		8.78%	0.4[0.22,0.72]
Sharma 2011	5/35	14/35		3.61%	0.36[0.14,0.88]
Sharma 2012	5/60	10/60		2.9%	0.5[0.18,1.38]
Simmons 1970	3/14	6/12		2.24%	0.43[0.14,1.36]
Uribe 1987a	1/22	3/23		0.62%	0.35[0.04,3.1]
Uribe 1987b	0/10	0/10			Not estimable
Watanabe 1997	0/41	0/34			Not estimable
Wen 2013	5/65	13/65		3.14%	0.38[0.15,1.02]
Xing 2003	0/23	2/22		0.33%	0.19[0.01,3.78]
Yao 2014	0/20	0/20			Not estimable
Zeng 2003	8/40	9/20		4.8%	0.44[0.2,0.98]
Ziada 2013	2/30	5/30		1.22%	0.4[0.08,1.9]
Subtotal (95% CI)	**768**	**719**		**50.38%**	**0.47[0.37,0.61]**
Total events: 76 (Disaccharide), 153 (Control)					
Heterogeneity: Tau²=0; Chi²=8.92, df=16(P=0.92); I²=0%					
Test for overall effect: Z=6.01(P<0.0001)					
1.12.2 Extreme worst-case scenario analysis					
Agrawal 2012	18/80	37/78		13.51%	0.47[0.3,0.76]
Corazza 1982	0/16	0/16			Not estimable
Dhiman 2000	2/14	3/12		1.14%	0.57[0.11,2.87]
Germain 1973	0/9	0/9			Not estimable
Horsmans 1997	0/7	0/7			Not estimable
Jain 2013	1/30	1/30		0.4%	1[0.07,15.26]
Li 1999	0/48	0/38			Not estimable
Mittal 2011	1/40	4/40		0.64%	0.25[0.03,2.14]
Prasad 2007	1/31	5/30		0.68%	0.19[0.02,1.56]
Quero 1997	1/20	0/20		0.3%	3[0.13,69.52]
Raza 2004	2/18	2/13		0.89%	0.72[0.12,4.48]
Riggio 2005	9/25	8/25		4.95%	1.13[0.52,2.44]
Sharma 2009	12/70	30/70		8.78%	0.4[0.22,0.72]
Sharma 2011	5/35	14/35		3.61%	0.36[0.14,0.88]
Sharma 2012	5/60	10/60		2.9%	0.5[0.18,1.38]
Simmons 1970	3/14	6/12		2.24%	0.43[0.14,1.36]
Uribe 1987a	1/22	3/23		0.62%	0.35[0.04,3.1]
Uribe 1987b	0/10	0/10			Not estimable
Watanabe 1997	0/41	0/34			Not estimable
Wen 2013	5/65	11/65		2.97%	0.45[0.17,1.24]
Xing 2003	0/23	2/22		0.33%	0.19[0.01,3.78]
Yao 2014	0/20	0/20			Not estimable
Zeng 2003	8/40	8/20		4.42%	0.5[0.22,1.14]
Ziada 2013	2/30	5/30		1.22%	0.4[0.08,1.9]
Subtotal (95% CI)	**768**	**719**		**49.62%**	**0.49[0.38,0.62]**
Total events: 76 (Disaccharide), 149 (Control)					
Heterogeneity: Tau²=0; Chi²=8.88, df=16(P=0.92); I²=0%					
Test for overall effect: Z=5.73(P<0.0001)					
Total (95% CI)	**1536**	**1438**		**100%**	**0.48[0.41,0.57]**
Total events: 152 (Disaccharide), 302 (Control)					
Heterogeneity: Tau²=0; Chi²=17.82, df=33(P=0.99); I²=0%					
Test for overall effect: Z=8.3(P<0.0001)					

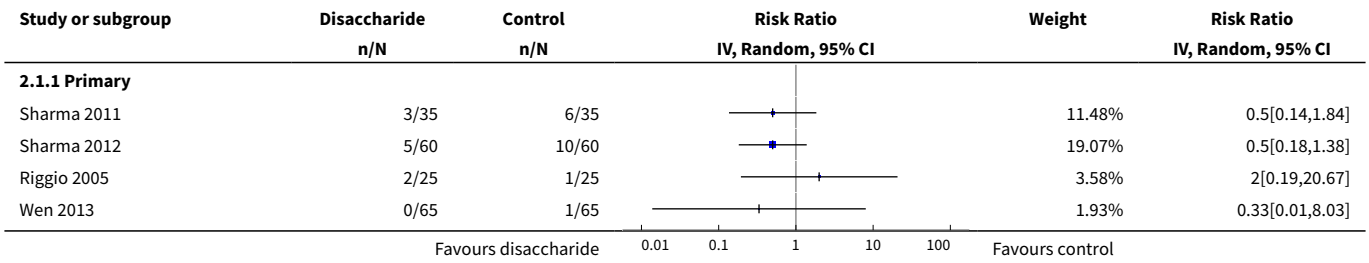


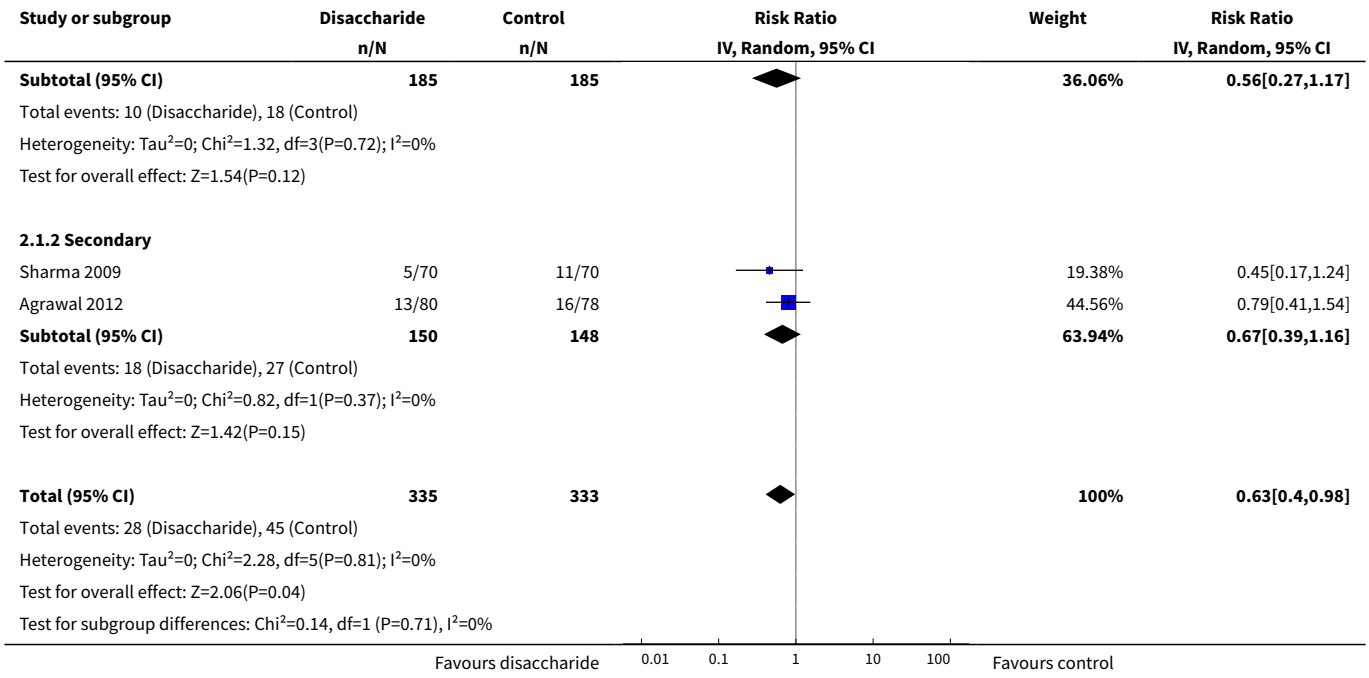


Comparison 2. Prevention trials: non-absorbable disaccharides versus placebo/no intervention

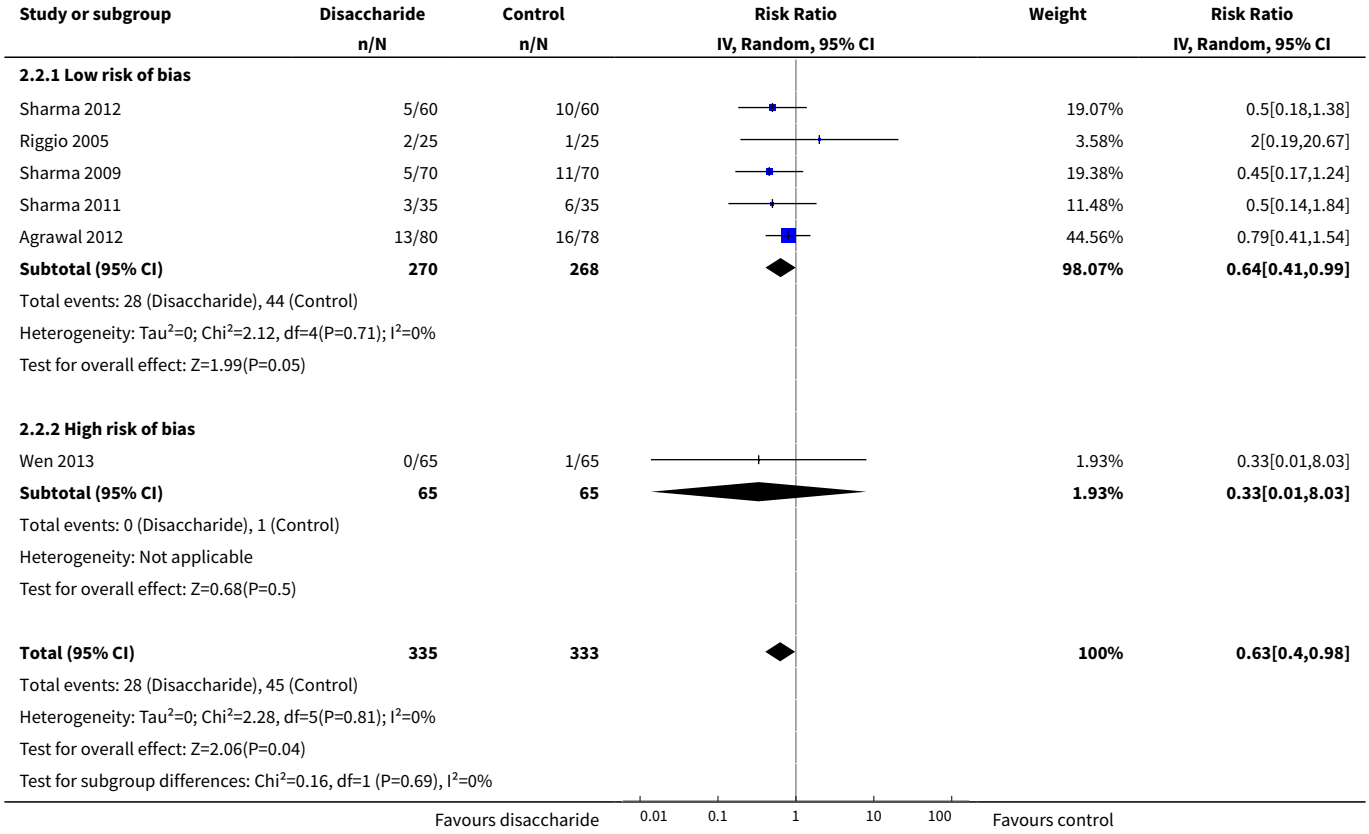
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	6	668	Risk Ratio (IV, Random, 95% CI)	0.63 [0.40, 0.98]
1.1 Primary	4	370	Risk Ratio (IV, Random, 95% CI)	0.56 [0.27, 1.17]
1.2 Secondary	2	298	Risk Ratio (IV, Random, 95% CI)	0.67 [0.39, 1.16]
2 Mortality and bias control	6	668	Risk Ratio (IV, Random, 95% CI)	0.63 [0.40, 0.98]
2.1 Low risk of bias	5	538	Risk Ratio (IV, Random, 95% CI)	0.64 [0.41, 0.99]
2.2 High risk of bias	1	130	Risk Ratio (IV, Random, 95% CI)	0.33 [0.01, 8.03]
3 Hepatic encephalopathy	6	668	Risk Ratio (IV, Random, 95% CI)	0.47 [0.33, 0.68]
3.1 Primary	4	370	Risk Ratio (IV, Random, 95% CI)	0.48 [0.23, 0.98]
3.2 Secondary	2	298	Risk Ratio (IV, Random, 95% CI)	0.44 [0.31, 0.64]
4 Serious adverse events	6	668	Risk Ratio (IV, Random, 95% CI)	0.48 [0.33, 0.70]
4.1 Primary prevention	4	370	Risk Ratio (IV, Random, 95% CI)	0.50 [0.24, 1.03]
4.2 Secondary prevention	2	298	Risk Ratio (IV, Random, 95% CI)	0.44 [0.31, 0.64]
5 Non-serious adverse events	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 2.1. Comparison 2 Prevention trials: non-absorbable disaccharides versus placebo/no intervention, Outcome 1 Mortality.



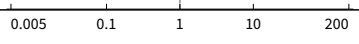


Analysis 2.2. Comparison 2 Prevention trials: non-absorbable disaccharides versus placebo/no intervention, Outcome 2 Mortality and bias control.



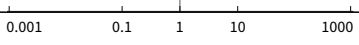
Analysis 2.3. Comparison 2 Prevention trials: non-absorbable disaccharides versus placebo/no intervention, Outcome 3 Hepatic encephalopathy.

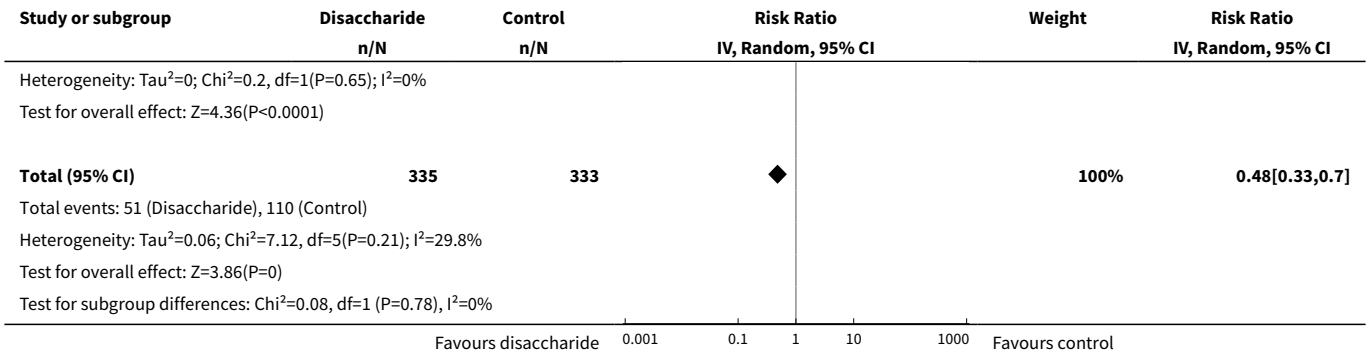
Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
2.3.1 Primary					
Riggio 2005	9/25	8/25		16.02%	1.13[0.52,2.44]
Sharma 2011	5/35	14/35		12.64%	0.36[0.14,0.88]
Sharma 2012	6/60	14/60		13.09%	0.43[0.18,1.04]
Wen 2013	2/65	11/65		5.61%	0.18[0.04,0.79]
Subtotal (95% CI)	**185**	**185**		**47.36%**	**0.48[0.23,0.98]**
Total events: 22 (Disaccharide), 47 (Control)					
Heterogeneity: Tau²=0.29; Chi²=6.62, df=3(P=0.09); I²=54.68%					
Test for overall effect: Z=2.02(P=0.04)					
2.3.2 Secondary					
Agrawal 2012	18/80	37/78		29.34%	0.47[0.3,0.76]
Sharma 2009	12/70	30/70		23.3%	0.4[0.22,0.72]
Subtotal (95% CI)	**150**	**148**		**52.64%**	**0.44[0.31,0.64]**
Total events: 30 (Disaccharide), 67 (Control)					
Heterogeneity: Tau²=0; Chi²=0.2, df=1(P=0.65); I²=0%					
Test for overall effect: Z=4.36(P<0.0001)					
Total (95% CI)	**335**	**333**		**100%**	**0.47[0.33,0.68]**
Total events: 52 (Disaccharide), 114 (Control)					
Heterogeneity: Tau²=0.06; Chi²=7.18, df=5(P=0.21); I²=30.31%					
Test for overall effect: Z=4.02(P<0.0001)					
Test for subgroup differences: Chi²=0.03, df=1 (P=0.86), I²=0%					



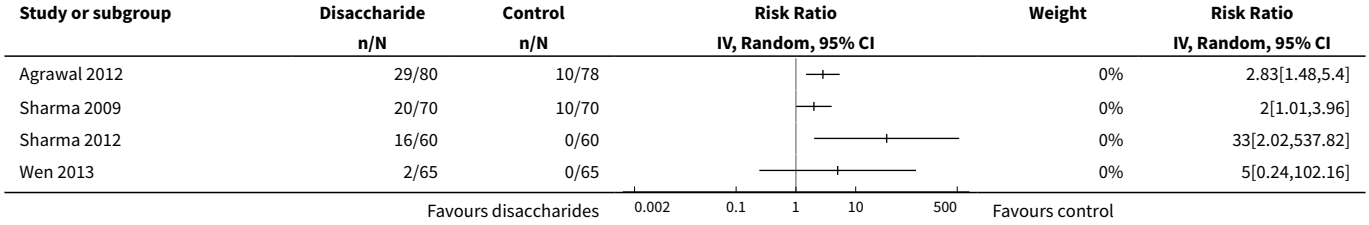
Analysis 2.4. Comparison 2 Prevention trials: non-absorbable disaccharides versus placebo/no intervention, Outcome 4 Serious adverse events.

Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
2.4.1 Primary prevention					
Riggio 2005	9/25	8/25		16.44%	1.13[0.52,2.44]
Sharma 2011	5/35	14/35		12.98%	0.36[0.14,0.88]
Sharma 2012	5/60	10/60		10.91%	0.5[0.18,1.38]
Wen 2013	2/65	11/65		5.77%	0.18[0.04,0.79]
Subtotal (95% CI)	**185**	**185**		**46.09%**	**0.5[0.24,1.03]**
Total events: 21 (Disaccharide), 43 (Control)					
Heterogeneity: Tau²=0.29; Chi²=6.37, df=3(P=0.09); I²=52.89%					
Test for overall effect: Z=1.88(P=0.06)					
2.4.2 Secondary prevention					
Agrawal 2012	18/80	37/78		30.03%	0.47[0.3,0.76]
Sharma 2009	12/70	30/70		23.87%	0.4[0.22,0.72]
Subtotal (95% CI)	**150**	**148**		**53.91%**	**0.44[0.31,0.64]**
Total events: 30 (Disaccharide), 67 (Control)					





Analysis 2.5. Comparison 2 Prevention trials: non-absorbable disaccharides versus placebo/no intervention, Outcome 5 Non-serious adverse events.



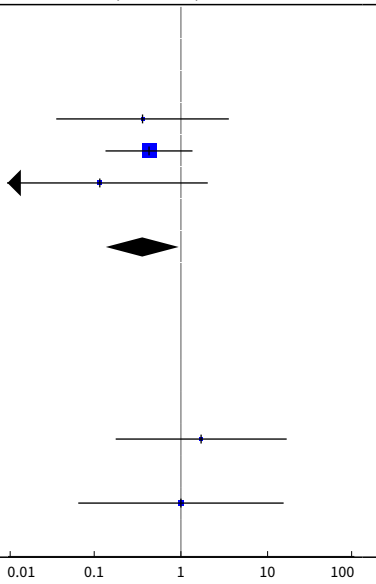
Comparison 3. Treatment trials: non-absorbable disaccharides versus placebo/no intervention

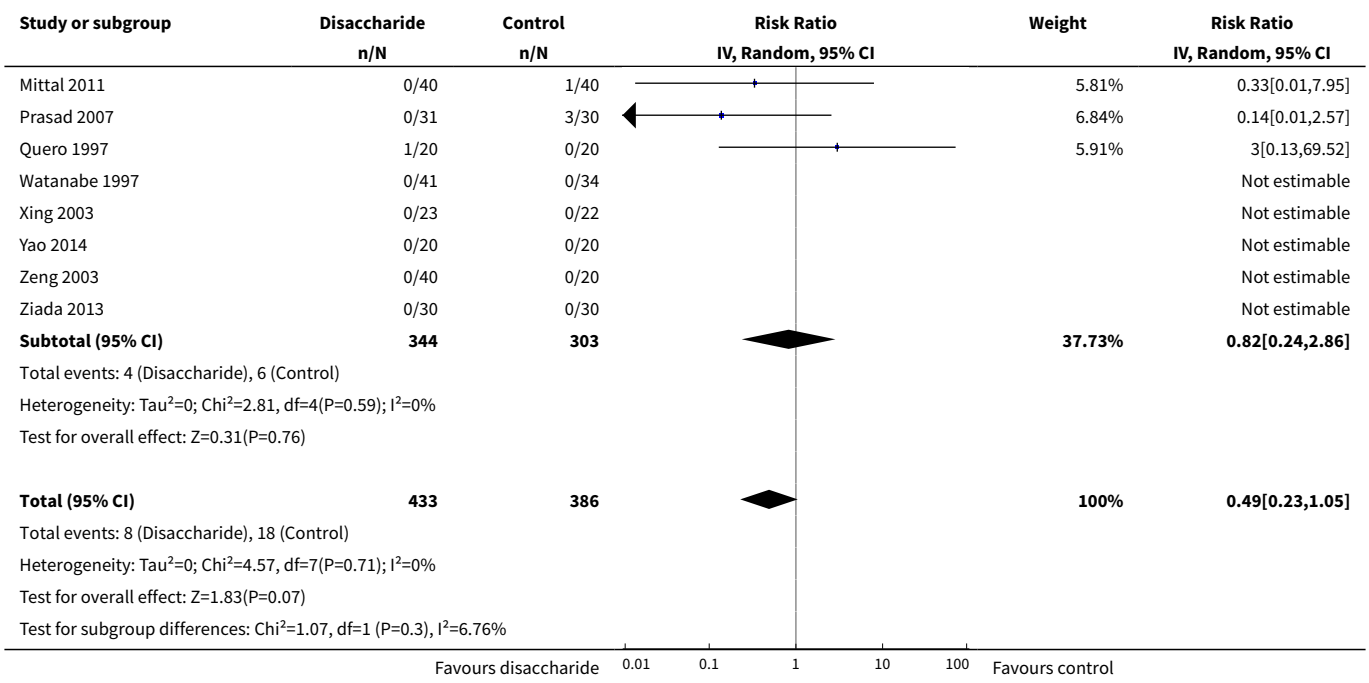
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	18	819	Risk Ratio (IV, Random, 95% CI)	0.49 [0.23, 1.05]
1.1 Overt	6	172	Risk Ratio (IV, Random, 95% CI)	0.36 [0.14, 0.94]
1.2 Minimal	12	647	Risk Ratio (IV, Random, 95% CI)	0.82 [0.24, 2.86]
2 Mortality in trials with a low risk of bias	18	819	Risk Ratio (IV, Random, 95% CI)	0.49 [0.23, 1.05]
2.1 Low risk of bias	3	167	Risk Ratio (IV, Random, 95% CI)	0.56 [0.12, 2.68]
2.2 High risk of bias	15	652	Risk Ratio (IV, Random, 95% CI)	0.47 [0.20, 1.13]
3 Mortality in acute or chronic hepatic encephalopathy	6	172	Risk Ratio (IV, Random, 95% CI)	0.36 [0.14, 0.94]
3.1 Acute	3	102	Risk Ratio (IV, Random, 95% CI)	0.36 [0.14, 0.94]
3.2 Chronic	3	70	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Hepatic encephalopathy	16	747	Risk Ratio (IV, Random, 95% CI)	0.63 [0.53, 0.74]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Overt	5	140	Risk Ratio (IV, Random, 95% CI)	0.62 [0.39, 0.99]
4.2 Minimal	11	607	Risk Ratio (IV, Random, 95% CI)	0.63 [0.52, 0.76]
5 Acute or chronic hepatic encephalopathy	5	140	Risk Ratio (IV, Random, 95% CI)	0.62 [0.39, 0.99]
5.1 Acute	3	102	Risk Ratio (IV, Random, 95% CI)	0.59 [0.34, 1.00]
5.2 Chronic	2	38	Risk Ratio (IV, Random, 95% CI)	0.55 [0.07, 4.10]
6 Serious adverse events	18	819	Risk Ratio (IV, Random, 95% CI)	0.42 [0.26, 0.69]
6.1 Overt	6	172	Risk Ratio (IV, Random, 95% CI)	0.40 [0.16, 1.02]
6.2 Minimal	12	647	Risk Ratio (IV, Random, 95% CI)	0.43 [0.24, 0.78]
7 Serious adverse events in acute or chronic hepatic encephalopathy	6	172	Risk Ratio (IV, Random, 95% CI)	0.40 [0.16, 1.02]
7.1 Acute	3	102	Risk Ratio (IV, Random, 95% CI)	0.40 [0.16, 1.02]
7.2 Chronic	3	70	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Non-serious adverse events	5	191	Risk Ratio (IV, Random, 95% CI)	2.12 [0.62, 7.28]

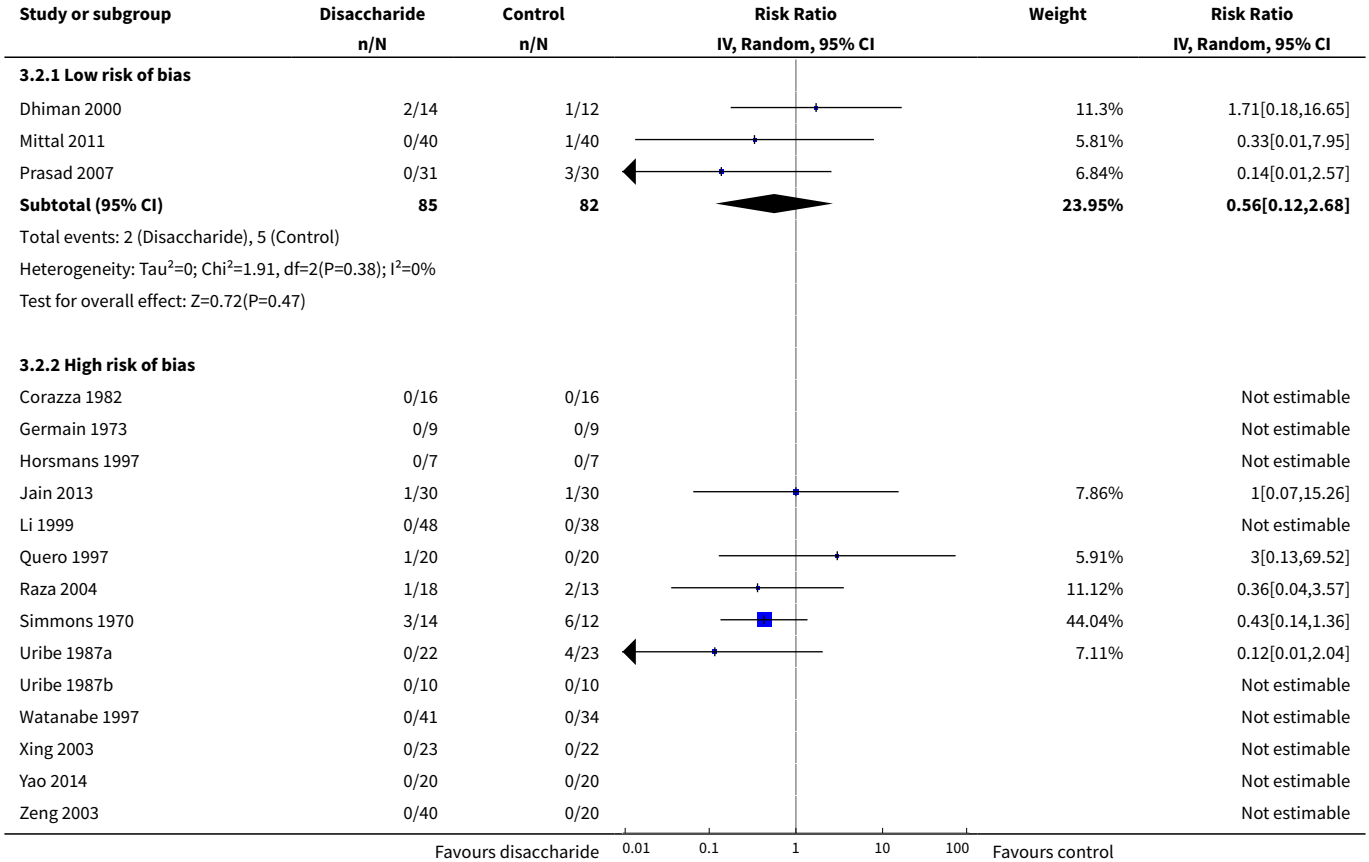
Analysis 3.1. Comparison 3 Treatment trials: non-absorbable disaccharides versus placebo/no intervention, Outcome 1 Mortality.

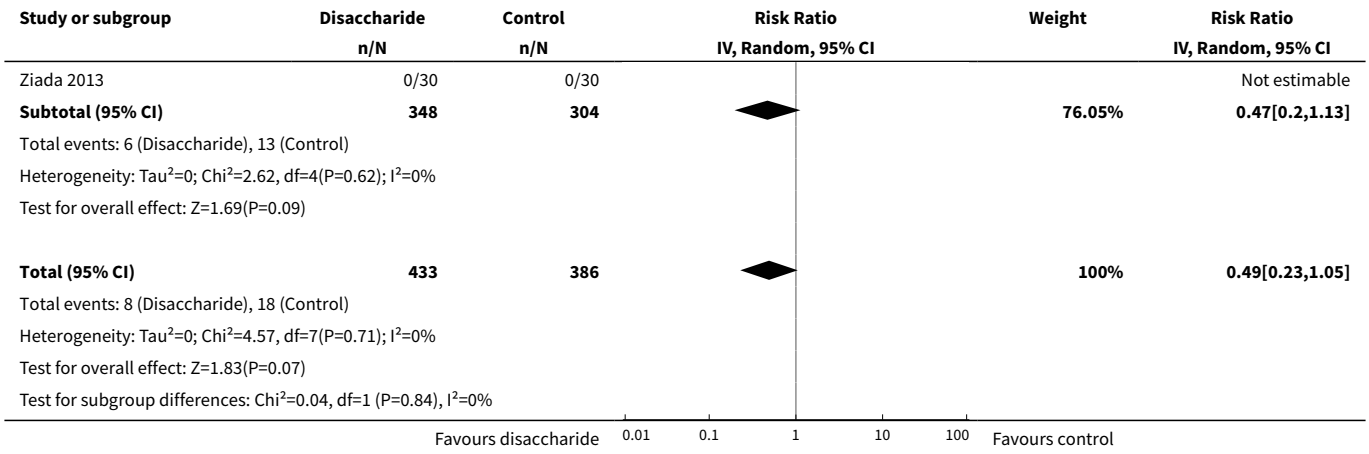
Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
3.1.1 Overt					
Corazza 1982	0/16	0/16			Not estimable
Germain 1973	0/9	0/9			Not estimable
Raza 2004	1/18	2/13		11.12%	0.36[0.04,3.57]
Simmons 1970	3/14	6/12		44.04%	0.43[0.14,1.36]
Uribe 1987a	0/22	4/23		7.11%	0.12[0.01,2.04]
Uribe 1987b	0/10	0/10			Not estimable
Subtotal (95% CI)	**89**	**83**		**62.27%**	**0.36[0.14,0.94]**
Total events: 4 (Disaccharide), 12 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.69, df=2(P=0.71); I^2=0%					
Test for overall effect: Z=2.08(P=0.04)					
3.1.2 Minimal					
Dhiman 2000	2/14	1/12		11.3%	1.71[0.18,16.65]
Horsmans 1997	0/7	0/7			Not estimable
Jain 2013	1/30	1/30		7.86%	1[0.07,15.26]
Li 1999	0/48	0/38			Not estimable



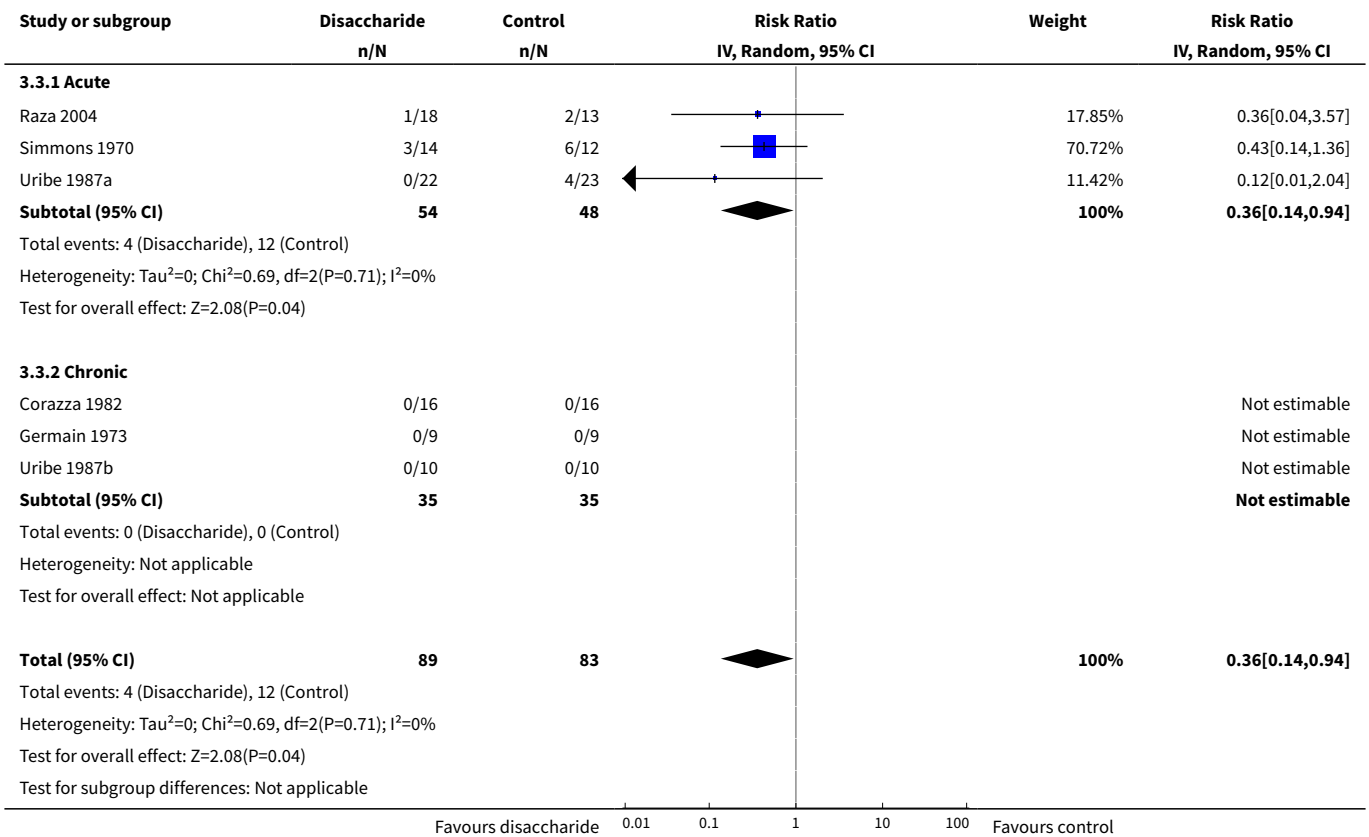


Analysis 3.2. Comparison 3 Treatment trials: non-absorbable disaccharides versus placebo/no intervention, Outcome 2 Mortality in trials with a low risk of bias.





Analysis 3.3. Comparison 3 Treatment trials: non-absorbable disaccharides versus placebo/no intervention, Outcome 3 Mortality in acute or chronic hepatic encephalopathy.



Analysis 3.4. Comparison 3 Treatment trials: non-absorbable disaccharides versus placebo/no intervention, Outcome 4 Hepatic encephalopathy.

Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
3.4.1 Overt					
Germain 1973	4/9	3/9		1.93%	1.33[0.41,4.33]
Raza 2004	7/18	8/13		4.65%	0.63[0.31,1.3]
Simmons 1970	4/14	5/12		2.33%	0.69[0.24,1.99]
Uribe 1987a	3/22	8/23		1.89%	0.39[0.12,1.29]
Uribe 1987b	1/10	6/10		0.75%	0.17[0.02,1.14]
Subtotal (95% CI)	**73**	**67**		**11.54%**	**0.62[0.39,0.99]**
Total events: 19 (Disaccharide), 30 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.01, df=4(P=0.4); I^2=0.37%					
Test for overall effect: Z=1.98(P=0.05)					
3.4.2 Minimal					
Dhiman 2000	6/14	12/12		6.46%	0.45[0.25,0.81]
Horsmans 1997	6/7	6/7		10.26%	1[0.65,1.53]
Jain 2013	2/30	2/30		0.78%	1[0.15,6.64]
Li 1999	22/48	28/38		12.63%	0.62[0.43,0.89]
Mittal 2011	21/40	36/40		14.79%	0.58[0.43,0.8]
Prasad 2007	6/31	20/30		4.23%	0.29[0.14,0.62]
Quero 1997	0/20	1/20		0.29%	0.33[0.01,7.72]
Watanabe 1997	13/41	12/34		5.67%	0.9[0.47,1.7]
Xing 2003	11/23	22/22		10.46%	0.49[0.32,0.75]
Zeng 2003	7/40	8/20		3.42%	0.44[0.18,1.03]
Ziada 2013	22/30	29/30		19.48%	0.76[0.61,0.95]
Subtotal (95% CI)	**324**	**283**		**88.46%**	**0.63[0.52,0.76]**
Total events: 116 (Disaccharide), 176 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=15.9, df=10(P=0.1); I^2=37.09%					
Test for overall effect: Z=4.81(P<0.0001)					
Total (95% CI)	**397**	**350**		**100%**	**0.63[0.53,0.74]**
Total events: 135 (Disaccharide), 206 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=19.95, df=15(P=0.17); I^2=24.82%					
Test for overall effect: Z=5.39(P<0.0001)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.97), I^2=0%					

Analysis 3.5. Comparison 3 Treatment trials: non-absorbable disaccharides versus placebo/no intervention, Outcome 5 Acute or chronic hepatic encephalopathy.

Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
3.5.1 Acute					
Raza 2004	7/18	8/13		42.6%	0.63[0.31,1.3]
Simmons 1970	4/14	5/12		19.63%	0.69[0.24,1.99]
Uribe 1987a	3/22	8/23		15.7%	0.39[0.12,1.29]
Subtotal (95% CI)	**54**	**48**		**77.93%**	**0.59[0.34,1]**
Total events: 14 (Disaccharide), 21 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.56, df=2(P=0.75); I^2=0%					

Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Test for overall effect: Z=1.96(P=0.05)					
3.5.2 Chronic					
Germain 1973	4/9	3/9		16.06%	1.33[0.41,4.33]
Uribe 1987b	1/10	6/10		6.01%	0.17[0.02,1.14]
Subtotal (95% CI)	**19**	**19**		**22.07%**	**0.55[0.07,4.1]**
Total events: 5 (Disaccharide), 9 (Control)					
Heterogeneity: Tau^2=1.5; Chi^2=3.26, df=1(P=0.07); I^2=69.29%					
Test for overall effect: Z=0.59(P=0.56)					
Total (95% CI)	**73**	**67**		**100%**	**0.62[0.39,0.99]**
Total events: 19 (Disaccharide), 30 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.01, df=4(P=0.4); I^2=0.37%					
Test for overall effect: Z=1.98(P=0.05)					
Test for subgroup differences: Chi^2=0, df=1 (P=0.95), I^2=0%					

Analysis 3.6. Comparison 3 Treatment trials: non-absorbable disaccharides versus placebo/no intervention, Outcome 6 Serious adverse events.

Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
3.6.1 Overt					
Corazza 1982	0/16	0/16			Not estimable
Germain 1973	0/9	0/9			Not estimable
Raza 2004	1/18	2/13		4.65%	0.36[0.04,3.57]
Simmons 1970	3/14	6/12		18.42%	0.43[0.14,1.36]
Uribe 1987a	1/22	3/23		5.11%	0.35[0.04,3.1]
Uribe 1987b	0/10	0/10			Not estimable
Subtotal (95% CI)	**89**	**83**		**28.19%**	**0.4[0.16,1.02]**
Total events: 5 (Disaccharide), 11 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=2(P=0.98); I^2=0%					
Test for overall effect: Z=1.92(P=0.05)					
3.6.2 Minimal					
Dhiman 2000	2/14	3/12		9.37%	0.57[0.11,2.87]
Horsmans 1997	0/7	0/7			Not estimable
Jain 2013	1/30	1/30		3.29%	1[0.07,15.26]
Li 1999	0/48	0/38			Not estimable
Mittal 2011	1/40	4/40		5.3%	0.25[0.03,2.14]
Prasad 2007	1/31	5/30		5.61%	0.19[0.02,1.56]
Quero 1997	1/20	0/20		2.47%	3[0.13,69.52]
Watanabe 1997	0/41	0/34			Not estimable
Xing 2003	0/23	2/22		2.75%	0.19[0.01,3.78]
Yao 2014	0/20	0/20			Not estimable
Zeng 2003	7/40	8/20		32.98%	0.44[0.18,1.03]
Ziada 2013	2/30	5/30		10.04%	0.4[0.08,1.9]
Subtotal (95% CI)	**344**	**303**		**71.81%**	**0.43[0.24,0.78]**
Total events: 15 (Disaccharide), 28 (Control)					

Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=3.05, df=7(P=0.88); I²=0%					
Test for overall effect: Z=2.81(P=0)					
Total (95% CI)	**433**	**386**		**100%**	**0.42[0.26,0.69]**
Total events: 20 (Disaccharide), 39 (Control)					
Heterogeneity: Tau²=0; Chi²=3.11, df=10(P=0.98); I²=0%					
Test for overall effect: Z=3.4(P=0)					
Test for subgroup differences: Chi²=0.02, df=1 (P=0.89), I²=0%					

Favours disaccharide 0.001 0.1 1 10 1000 Favours control

Analysis 3.7. Comparison 3 Treatment trials: non-absorbable disaccharides versus placebo/no intervention, Outcome 7 Serious adverse events in acute or chronic hepatic encephalopathy.

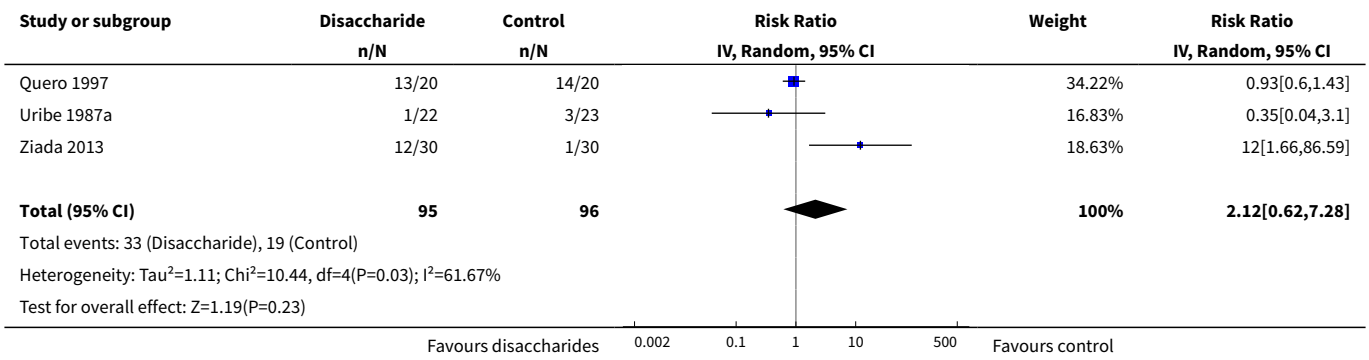
Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
3.7.1 Acute					
Raza 2004	1/18	2/13		16.5%	0.36[0.04,3.57]
Simmons 1970	3/14	6/12		65.36%	0.43[0.14,1.36]
Uribe 1987a	1/22	3/23		18.13%	0.35[0.04,3.1]
Subtotal (95% CI)	**54**	**48**		**100%**	**0.4[0.16,1.02]**
Total events: 5 (Disaccharide), 11 (Control)					
Heterogeneity: Tau²=0; Chi²=0.04, df=2(P=0.98); I²=0%					
Test for overall effect: Z=1.92(P=0.05)					
3.7.2 Chronic					
Corazza 1982	0/16	0/16			Not estimable
Germain 1973	0/9	0/9			Not estimable
Uribe 1987b	0/10	0/10			Not estimable
Subtotal (95% CI)	**35**	**35**			**Not estimable**
Total events: 0 (Disaccharide), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**89**	**83**		**100%**	**0.4[0.16,1.02]**
Total events: 5 (Disaccharide), 11 (Control)					
Heterogeneity: Tau²=0; Chi²=0.04, df=2(P=0.98); I²=0%					
Test for overall effect: Z=1.92(P=0.05)					
Test for subgroup differences: Not applicable					

Favours disaccharide 0.001 0.1 1 10 1000 Favours control

Analysis 3.8. Comparison 3 Treatment trials: non-absorbable disaccharides versus placebo/no intervention, Outcome 8 Non-serious adverse events.

Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Horsmans 1997	3/7	0/7		12.59%	7[0.43,114.7]
McClain 1984	4/16	1/16		17.73%	4[0.5,31.98]

Favours disaccharides 0.002 0.1 1 10 500 Favours control



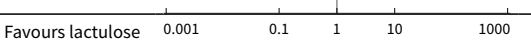
Comparison 4. Lactulose versus lactitol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	8	225	Risk Ratio (IV, Random, 95% CI)	1.30 [0.59, 2.85]
1.1 Overt hepatic encephalopathy	6	174	Risk Ratio (IV, Random, 95% CI)	1.30 [0.59, 2.85]
1.2 Minimal hepatic encephalopathy	1	20	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Prevention of hepatic encephalopathy	1	31	Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Hepatic encephalopathy	7	194	Risk Ratio (IV, Random, 95% CI)	1.00 [0.84, 1.19]
2.1 Overt hepatic encephalopathy	5	162	Risk Ratio (IV, Random, 95% CI)	1.08 [0.60, 1.96]
2.2 Minimal hepatic encephalopathy	1	20	Risk Ratio (IV, Random, 95% CI)	1.0 [0.83, 1.20]
2.3 Prevention hepatic encephalopathy	1	12	Risk Ratio (IV, Random, 95% CI)	0.20 [0.01, 3.46]
3 Serious adverse events	9	245	Risk Ratio (IV, Random, 95% CI)	1.56 [0.84, 2.88]
4 Non-serious adverse events	6		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1 Overall	6	169	Risk Ratio (IV, Random, 95% CI)	1.55 [0.88, 2.74]
4.2 Diarrhoea	3	61	Risk Ratio (IV, Random, 95% CI)	0.80 [0.39, 1.64]
4.3 Bloating and flatulence	4	128	Risk Ratio (IV, Random, 95% CI)	2.20 [1.06, 4.54]
4.4 Nausea	4	104	Risk Ratio (IV, Random, 95% CI)	3.20 [0.76, 13.43]
4.5 Hyponatraemia	1	25	Risk Ratio (IV, Random, 95% CI)	3.23 [0.14, 72.46]
4.6 Abdominal pain	3	91	Risk Ratio (IV, Random, 95% CI)	0.95 [0.47, 1.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.7 Asthenia	1	31	Risk Ratio (IV, Random, 95% CI)	0.35 [0.02, 8.08]
5 Number Connection Test: end of treatment	4	84	Mean Difference (IV, Random, 95% CI)	-4.22 [-16.12, 7.68]
6 Number Connection Test: change from baseline	1	25	Mean Difference (IV, Random, 95% CI)	0.20 [-0.54, 0.94]
7 Venous blood ammonia: end of treatment	3	72	Mean Difference (IV, Random, 95% CI)	6.47 [-8.36, 21.29]
8 Venous blood ammonia: change from baseline	1	25	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.80, 0.40]

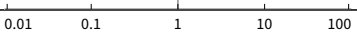
Analysis 4.1. Comparison 4 Lactulose versus lactitol, Outcome 1 Mortality.

Study or subgroup	Lactulose n/N	Lactitol n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
4.1.1 Overt hepatic encephalopathy					
Grandi 1991	0/20	0/20			Not estimable
Heredia 1987	4/20	3/20		33.18%	1.33[0.34,5.21]
Jankovic 1996	2/9	1/7		12.87%	1.56[0.17,13.87]
Morgan 1987a	4/12	4/13		47.21%	1.08[0.35,3.4]
Morgan 1987b	1/6	0/6		6.74%	3[0.15,61.74]
Pai 1995	0/20	0/21			Not estimable
Subtotal (95% CI)	**87**	**87**		**100%**	**1.3[0.59,2.85]**
Total events: 11 (Lactulose), 8 (Lactitol)					
Heterogeneity: Tau^2=0; Chi^2=0.42, df=3(P=0.94); I^2=0%					
Test for overall effect: Z=0.66(P=0.51)					
4.1.2 Minimal hepatic encephalopathy					
Morgan 1989	0/10	0/10			Not estimable
Subtotal (95% CI)	**10**	**10**			**Not estimable**
Total events: 0 (Lactulose), 0 (Lactitol)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.1.3 Prevention of hepatic encephalopathy					
Riggio 1989	0/15	0/16			Not estimable
Subtotal (95% CI)	**15**	**16**			**Not estimable**
Total events: 0 (Lactulose), 0 (Lactitol)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**112**	**113**		**100%**	**1.3[0.59,2.85]**
Total events: 11 (Lactulose), 8 (Lactitol)					
Heterogeneity: Tau^2=0; Chi^2=0.42, df=3(P=0.94); I^2=0%					
Test for overall effect: Z=0.66(P=0.51)					
Test for subgroup differences: Not applicable					



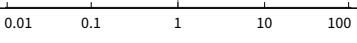
Analysis 4.2. Comparison 4 Lactulose versus lactitol, Outcome 2 Hepatic encephalopathy.

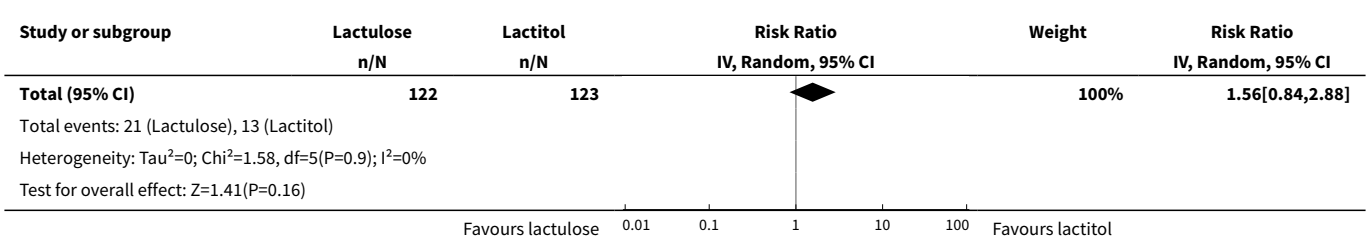
Study or subgroup	Lactulose n/N	Lactitol n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
4.2.1 Overt hepatic encephalopathy					
Grandi 1991	5/20	4/20		2.25%	1.25[0.39,3.99]
Heredia 1987	4/20	3/20		1.63%	1.33[0.34,5.21]
Morgan 1987a	4/12	5/13		2.72%	0.87[0.3,2.49]
Morgan 1987b	0/6	0/6			Not estimable
Pai 1995	4/22	4/23		1.92%	1.05[0.3,3.67]
Subtotal (95% CI)	**80**	**82**		**8.53%**	**1.08[0.6,1.96]**
Total events: 17 (Lactulose), 16 (Lactitol)					
Heterogeneity: Tau²=0; Chi²=0.32, df=3(P=0.96); I²=0%					
Test for overall effect: Z=0.26(P=0.8)					
4.2.2 Minimal hepatic encephalopathy					
Morgan 1989	10/10	10/10		91.1%	1[0.83,1.2]
Subtotal (95% CI)	**10**	**10**		**91.1%**	**1[0.83,1.2]**
Total events: 10 (Lactulose), 10 (Lactitol)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.2.3 Prevention hepatic encephalopathy					
Riggio 1989	0/6	2/6		0.37%	0.2[0.01,3.46]
Subtotal (95% CI)	**6**	**6**		**0.37%**	**0.2[0.01,3.46]**
Total events: 0 (Lactulose), 2 (Lactitol)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=1.11(P=0.27)					
Total (95% CI)	**96**	**98**		**100%**	**1[0.84,1.19]**
Total events: 27 (Lactulose), 28 (Lactitol)					
Heterogeneity: Tau²=0; Chi²=1.61, df=5(P=0.9); I²=0%					
Test for overall effect: Z=0.01(P=0.99)					
Test for subgroup differences: Chi²=1.29, df=1 (P=0.52), I²=0%					



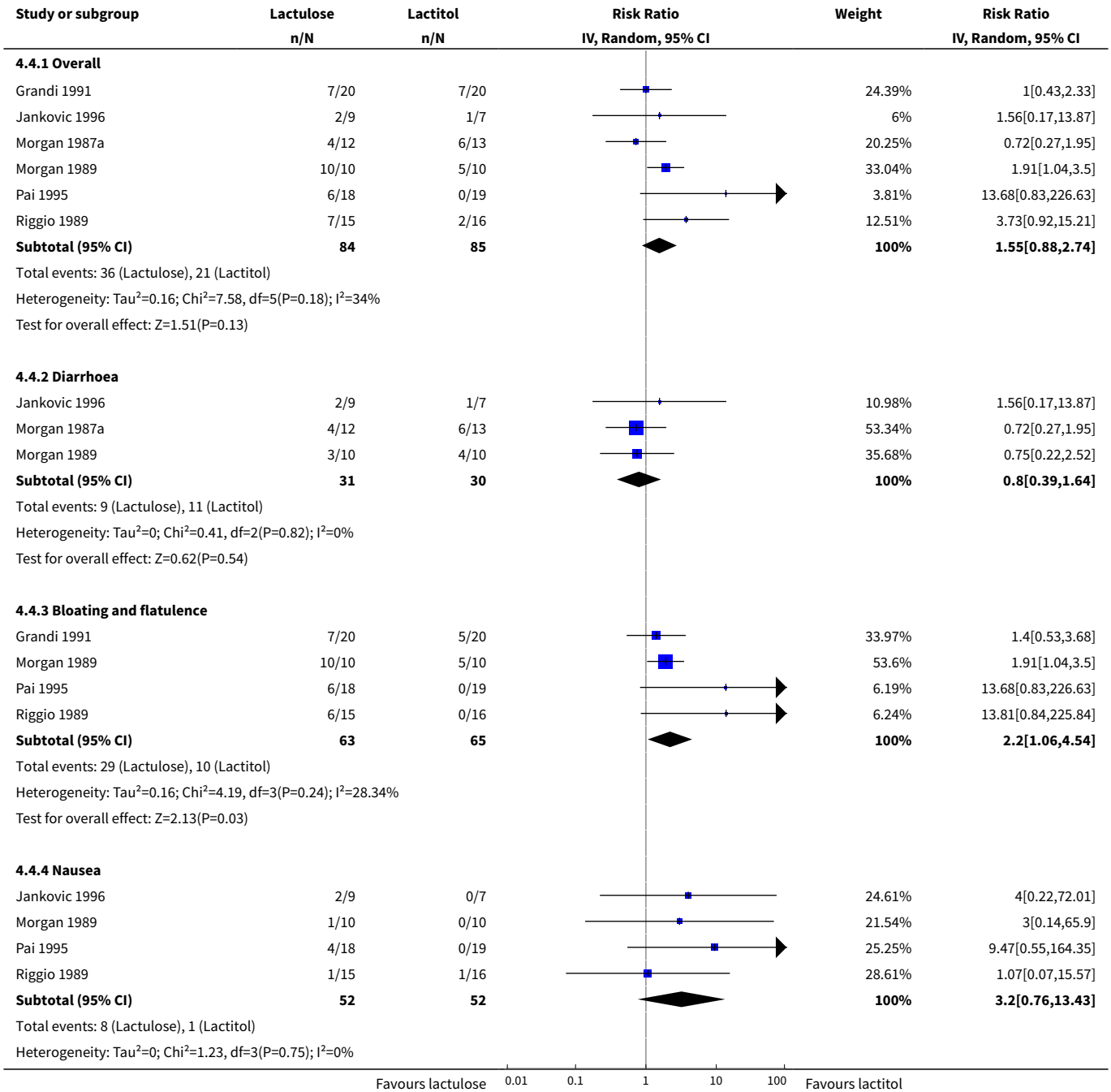
Analysis 4.3. Comparison 4 Lactulose versus lactitol, Outcome 3 Serious adverse events.

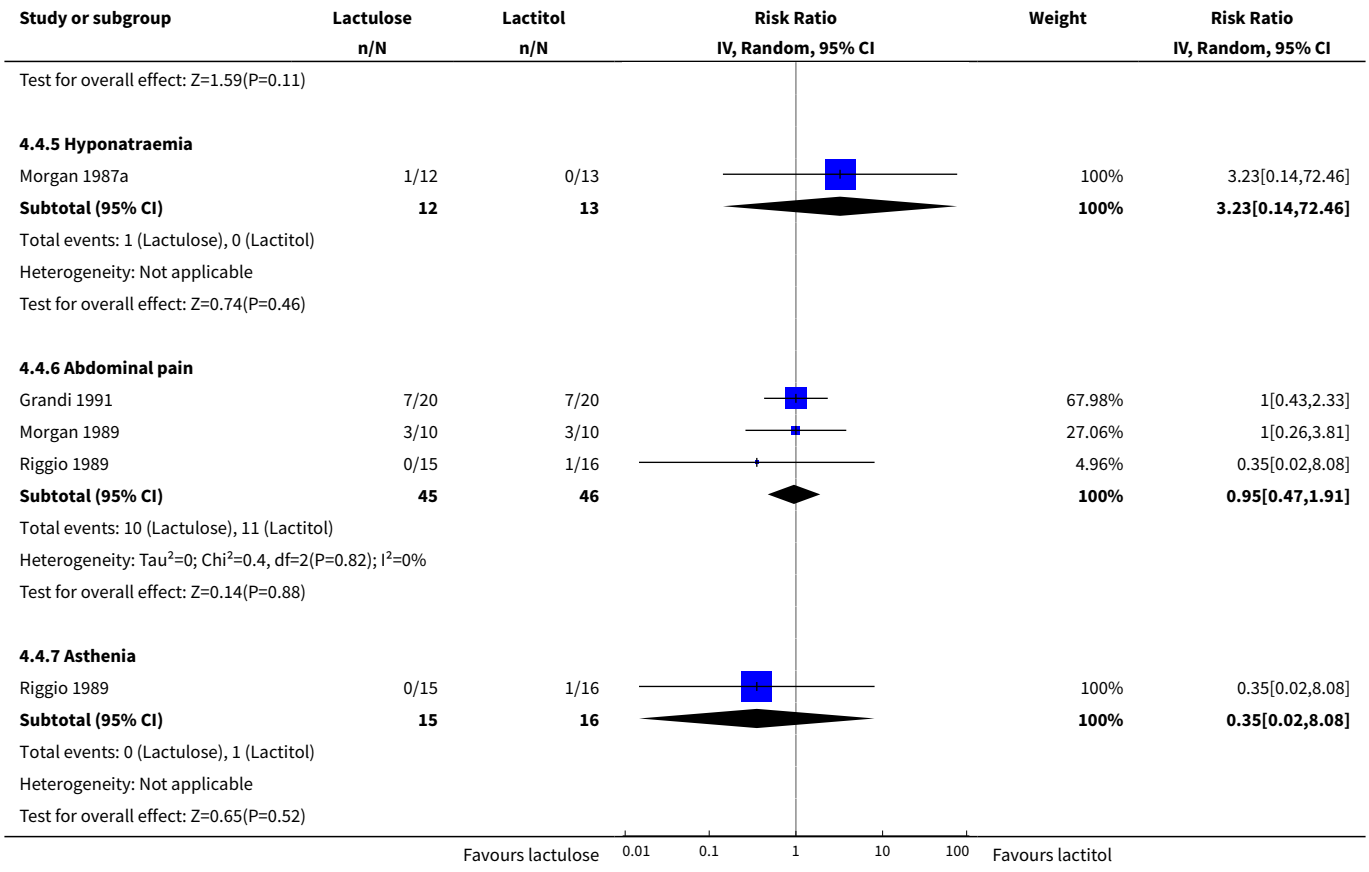
Study or subgroup	Lactulose n/N	Lactitol n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Grandi 1991	0/20	0/20			Not estimable
Heredia 1987	4/20	3/20		20.34%	1.33[0.34,5.21]
Heredia 1988	0/10	0/10			Not estimable
Jankovic 1996	2/9	1/7		7.89%	1.56[0.17,13.87]
Morgan 1987a	4/12	1/13		9.02%	4.33[0.56,33.53]
Morgan 1987b	1/6	0/6		4.13%	3[0.15,61.74]
Morgan 1989	0/10	0/10			Not estimable
Pai 1995	4/20	4/21		24.43%	1.05[0.3,3.64]
Riggio 1989	6/15	4/16		34.19%	1.6[0.56,4.58]



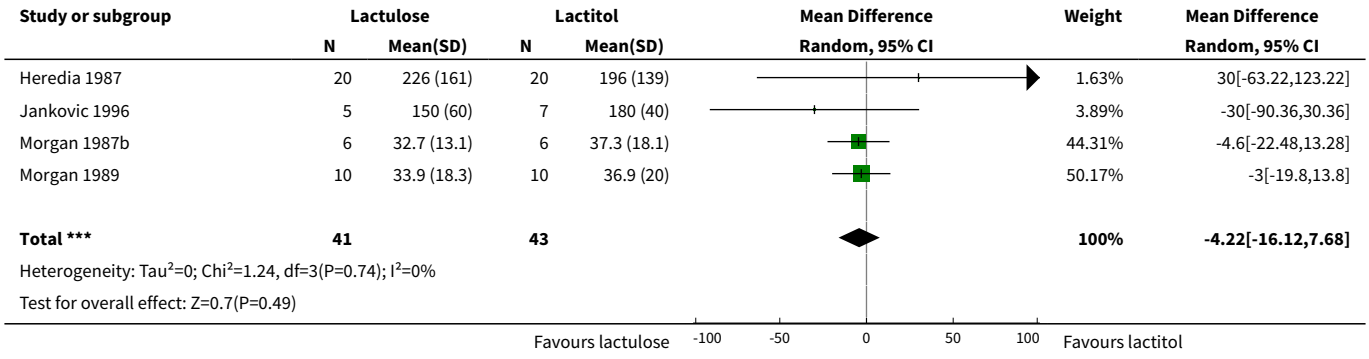


Analysis 4.4. Comparison 4 Lactulose versus lactitol, Outcome 4 Non-serious adverse events.

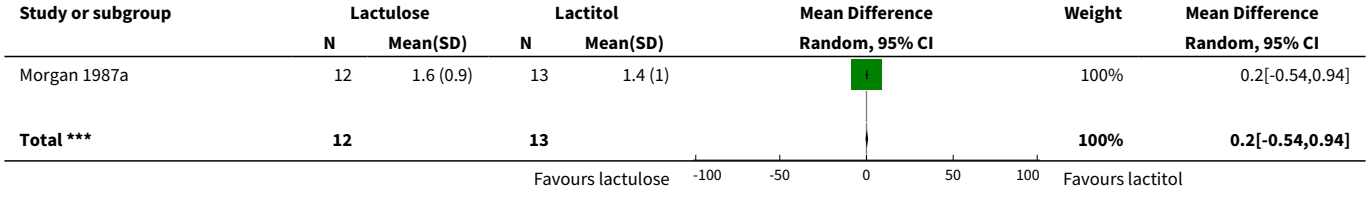


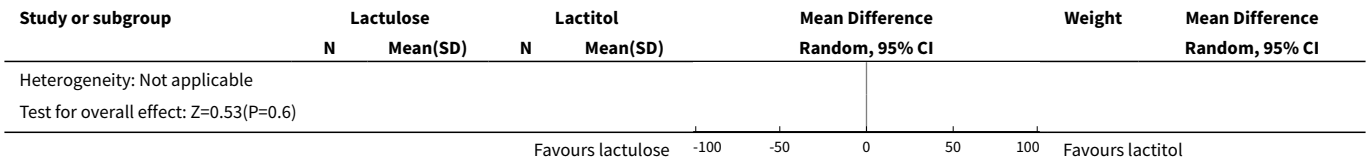


Analysis 4.5. Comparison 4 Lactulose versus lactitol, Outcome 5 Number Connection Test: end of treatment.

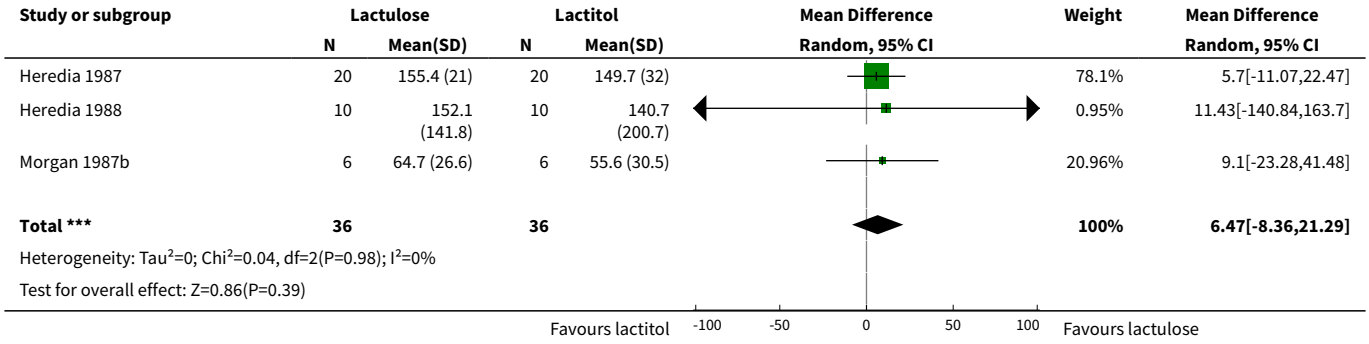


Analysis 4.6. Comparison 4 Lactulose versus lactitol, Outcome 6 Number Connection Test: change from baseline.

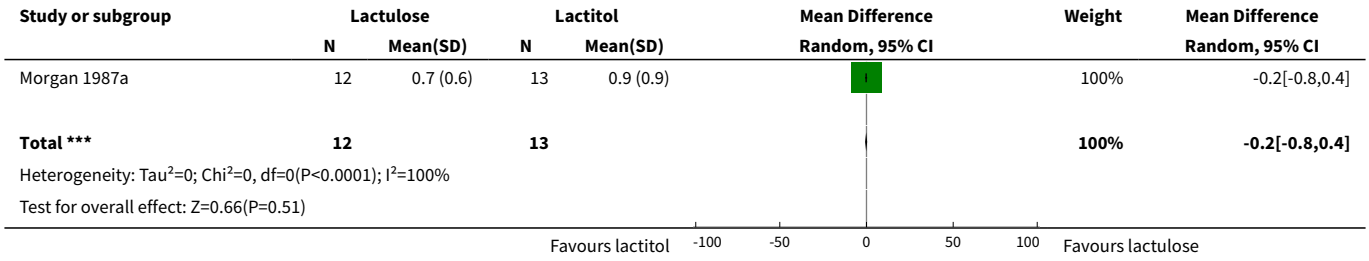




Analysis 4.7. Comparison 4 Lactulose versus lactitol, Outcome 7 Venous blood ammonia: end of treatment.



Analysis 4.8. Comparison 4 Lactulose versus lactitol, Outcome 8 Venous blood ammonia: change from baseline.



ADDITIONAL TABLES

Table 1. Definitions and assessment of overt hepatic encephalopathy with corresponding recommended definitions in the EASL/AASLD guidelines

Trial	Definition in trial publication	Definition based on classification in EASL/AASLD guidelines	Assessment of hepatic encephalopathy
Elkington 1969	Chronic persistent hepatic encephalopathy	Persistent	Mental status assessed using Parsons-Smith criteria Arterial blood ammonia concentrations Electroencephalogram

Table 1. Definitions and assessment of overt hepatic encephalopathy with corresponding recommended definitions in the EASL/AASLD guidelines *(Continued)*

Simmons 1970	Acute, acute remittent, and chronic remittent hepatic encephalopathy	Episodic (81%) Recurrent (19%)	Mental status assessed on a scale similar to but more extensive than the West Haven Criteria Venous blood ammonia concentrations
Brown 1971	Chronic persistent hepatic encephalopathy	Persistent	Mental status Blood ammonia concentrations Electroencephalogram*
Germain 1973	Chronic persistent hepatic encephalopathy	Persistent	Mental status assessed using Parson-Smith criteria Psychometric tests Venous blood ammonia concentrations Electroencephalogram
Rodgers 1973	Chronic persistent hepatic encephalopathy	Persistent	Clinical assessment of mental status Blood ammonia concentrations Electroencephalogram*
Corazza 1982	Chronic persistent hepatic encephalopathy	Persistent	Encephalopathy Intensity Score Plasma ammonia concentrations
Heredia 1987	Acute hepatic encephalopathy	Episodic/recurrent	Conn score Number Connection Test Blood ammonia concentrations Electroencephalogram
Morgan 1987a	Acute hepatic encephalopathy	Episodic	Portal Systemic Encephalopathy Sum and Index
Morgan 1987b	Chronic persistent hepatic encephalopathy	Persistent	Portal Systemic Encephalopathy Sum and Index
Uribe 1987a	Acute hepatic encephalopathy	Episodic	Portal Systemic Encephalopathy Sum and Index
Uribe 1987b	Chronic persistent hepatic encephalopathy	Persistent	Portal Systemic Encephalopathy Sum and Index
Heredia 1988	Chronic recurrent hepatic encephalopathy	Persistent	Portal Systemic Encephalopathy Sum and Index*
Grandi 1991	Chronic hepatic encephalopathy	Persistent	Portal Systemic Encephalopathy Sum and Index modified by omitting the electroencephalogram
Pai 1995	Acute hepatic encephalopathy	Episodic	Portal Systemic Encephalopathy Sum and Index
Jankovic 1996	Acute hepatic encephalopathy	Episodic	Mental status using West Haven criteria

Table 1. Definitions and assessment of overt hepatic encephalopathy with corresponding recommended definitions in the EASL/AASLD guidelines *(Continued)*

			Number connection Test A Electroencephalogram*
Raza 2004	Acute hepatic encephalopathy	Episodic	Clinical scoring Modified Portal Systemic Encephalopathy Sum and Index with electroencephalogram omitted and Digit Symbol test replacing Number Connection Test A

*The trial is not included in the analysis of hepatic encephalopathy, because we were unable to extract data on the number of participants with (or without) an overall improvement.

Table 2. Liver-related serious adverse events

Event	Non-absorbable disaccharides	Placebo/no intervention
Variceal bleeding	19/438 (4%)	17/336 (5%)
Hepatorenal syndrome	10/196 (5%)	7/153 (5%)
Spontaneous bacterial peritonitis	10/140 (7%)	16/138 (12%)
Liver failure	9/189 (5%)	7/117 (6%)

The overall risk of serious adverse events is analysed as one of the primary outcomes.

Table 3. Quero 1996: Sickness Impact Profile selected subscores

End of treatment	Control (n = 21)		Lactulose (n = 19)	
	Mean	Standard deviation	Mean	Standard deviation
Psychological subscore	8.0	11	10.9	14
Physical subscore	2.8	4	4.8	6

Table 4. Prasad 2007: Sickness Impact Profile selected subscores

Change from baseline	Control (n = 20)		Lactulose (n = 25)	
	Mean	Standard deviation	Mean	Standard deviation
Psychosocial scales				
Social interactions	0.5	0.68	8.5	1.35
Alertness	-0.75	1.13	10.43	1.73
Emotional behaviour	2.76	1.83	8.98	1.55

Table 4. Prasad 2007: Sickness Impact Profile selected subscores *(Continued)*

Communication	0.75	1.19	2.66	1.22
Total psychological subscore	0.77	0.41	8.47	0.98
Physical scales				
Ambulation	-1.89	1.12	3.67	0.80
Mobility	1.22	1.18	5.36	1.35
Body care and movements	0.72	0.42	1.62	0.55
Total physical subscore	0.01	0.52	2.99	0.56
Independent scales				
Sleep and rest	2.29	1.35	9.04	1.95
Work	-0.06	1.44	15.83	4.45
Home management	0.94	1.19	12.64	2.71
Recreation and pastimes	-0.28	1.11	11.59	1.97
Eating	-0.56	1.31	3.88	1.21

Table 5. Mittal 2009: Sickness Impact Profile selected subscores

Change from baseline	**Control (n = 31)**		**Lactulose (n = 35)**	
	Mean	Standard deviation	Mean	Standard deviation
Subscores				
Sleep and rest	2.87	6.5	11.64	5.5
Emotional behaviour	0.40	4.1	9.84	4.8
Body care and movements	–0.38	1.9	3.20	2.4
Home management	–0.25	5.7	6.34	5.20
Mobility	0.59	5.5	4.64	4.3
Social interaction	1.63	3.2	3.88	2.8
Alertness	0.18	2.4	3.63	2.2
Ambulation	–0.18	2.9	5.10	4.2
Communication	0.80	3.3	2.07	5.1
Work	0.64	2.5	9.46	15.7

Table 5. Mittal 2009: Sickness Impact Profile selected subscores *(Continued)*

Recreation and pastime	3.06	4.4	7.74	5.7
Eating	1.12	3.1	2.48	3.1
Psychosocial	1.13	2.4	5.17	2.9
Physical	–0.05	2.0	3.59	2.1

Table 6. Zeng 2003: WHO-Bref selected subscores

End of treatment	Control (n = 20)		Short term lactulose (n = 20)		Long-term lactulose (n = 20)	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Physical health	28	19	37	18	54	19
Psychological health	42	14	44	15	58	15
Social relationships	38	16	42	15	60	17
Environment	51	18	53	15	51	13

APPENDICES

Appendix 1. Search strategy

Database	Time span	Search terms
The Cochrane Hepato-Biliary Group Controlled Trials Register	October 2015	(disaccharid* or lactulos* or lactitol*) AND (encephalopath* OR liver disease* OR cirrho*)
Cochrane Central Register of Controlled Trials (CENTRAL)	Issue 10 of 12, 2015	#1 MeSH descriptor: [Disaccharides] explode all trees #2 MeSH descriptor: [Lactulose] explode all trees #3 disaccharid* or lactulos* or lactitol* #4 #1 or #2 or #3 #5 MeSH descriptor: [Hepatic Encephalopathy] explode all trees #6 MeSH descriptor: [Liver Diseases] explode all trees #7 MeSH descriptor: [Fibrosis] explode all trees #8 encephalopath* or liver disease* or cirrho* #9 #5 or #6 or #7 or #8 #10 #4 and #9

(Continued)

MEDLINE (Ovid SP)	1946 to October 2015	1. exp Disaccharides/ 2. exp Lactulose/ 3. (disaccharid* or lactulos* or lactitol*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 4. 1 or 2 or 3 5. exp Hepatic Encephalopathy/ 6. exp Liver Diseases/ 7. exp Fibrosis/ 8. (encephalopath* or liver disease* or cirrho*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 9. 5 or 6 or 7 or 8 10. 4 and 9 11. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 12. 10 and 11
Embase (Ovid SP)	1974 to October 2015	1. exp disaccharide/ 2. exp lactulose/ 3. exp lactitol/ 4. (disaccharid* or lactulos* or lactitol*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 5. 1 or 2 or 3 or 4 6. exp hepatic encephalopathy/ 7. exp liver disease/ 8. exp fibrosis/ 9. (encephalopath* or liver disease* or cirrho*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 10. 6 or 7 or 8 or 9 11. 5 and 10 12. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 13. 11 and 12

(Continued)

Science Citation Index Expanded (Web of Science)	1900 to October 2015	5 #4 AND #3 4 TS=(random* or blind* or placebo* or meta-analysis) 3 #2 AND #1 2 TS=(encephalopath* or liver disease* or cirrho*) 1 TS=(disaccharid* or lactulos* or lactitol*)

WHAT'S NEW

Date	Event	Description
19 April 2016	Amended	Reference Gluud 2016 added to Other published versions of this review.
28 February 2016	Amended	Changes to the 'Risk of bias' assessment: We updated the 'Risk of bias' assessment included in the latest version of the review. The change included the addition of the domains 'for-profit funding' and 'overall bias assessment'. We made the updates following the recommendations in the Cochrane Hepato-Biliary Group module.
30 September 2015	New search has been performed	The first version of this review, published in 2000, included 10 randomised clinical trials (RCTs) evaluating non-absorbable disaccharides versus placebo/no intervention and eight RCTs evaluating lactulose versus lactitol. An update in 2004 did not identify additional RCTs. This updated review includes 38 RCTs (29 evaluating non-absorbable disaccharides versus placebo/no intervention and nine evaluating lactulose versus lactitol). The methods of the review have been updated in accordance with the recommendations made in the *Cochrane Handbook for Systematic Reviews of Interventions* and the Cochrane Hepato-Biliary Group module. The changes include updated trial searches (the searches now include several trial registries), assessment of bias control and statistical analyses (regression analyses of small study effects, meta-regression analyses and Trial Sequential Analyses). The review includes 'Summary of findings' tables.
26 February 2015	New citation required and conclusions have changed	The updated review found evidence that lactulose and lactitol are associated with beneficial effects on mortality, hepatic encephalopathy, and serious adverse events.
26 February 2015	New search has been performed	We excluded RCTs evaluating antibiotics for people with hepatic encephalopathy to avoid overlap with another planned review (Kimer 2015). Hence, we changed the review title 'Nonabsorbable disaccharides for hepatic encephalopathy' (Als-Nielsen 2000; Als-Nielsen 2004a; Als-Nielsen 2004b; Als-Nielsen 2005) to 'Non-absorbable disaccharides versus placebo/no intervention and lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis'.

CONTRIBUTIONS OF AUTHORS

LL Gluud drafted the revised review, identified and selected RCTs, contributed to the data extraction, analyses, and interpretation of the results, and revised the review. H Vilstrup identified and selected RCTs, contributed to the data extraction, analyses, and interpretation of the results, and revised the review. MY Morgan identified and selected RCTs, contributed to the data extraction, analyses, and interpretation of the results, and revised the review.

All authors agreed to the publication of the review.

DECLARATIONS OF INTEREST

Lise L Gluud received payment for presentations given at scientific meetings sponsored by Norgine.

All review authors have conducted previous reviews on hepatic encephalopathy and two authors (Hendrik Vilstrup and Marsha Morgan) have conducted RCTs on hepatic encephalopathy. These previous research activities are an academic bias based on the definitions given in the Cochrane Hepato-Biliary Group module.

SOURCES OF SUPPORT

Internal sources

- No funding received, Other.

External sources

- No funding received, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have revised the methods used in the original protocol and the previous version of this review (Als-Nielsen 2000; Als-Nielsen 2004a; Als-Nielsen 2004b; Als-Nielsen 2005) with:

- exclusion of RCTs assessing non-absorbable disaccharides versus antibiotics;
- redefinition of primary and secondary outcomes (serious adverse events was previously a secondary outcome and is now a primary outcome);
- revised assessment of bias control based on the Cochrane Hepato-Biliary Group module (Gluud 2015). The changes include the addition of the domains missing outcome data; outcome reporting bias; other bias; for-profit funding; overall bias assessment.
- additional statistical analyses including regression analyses of small study effects; trial sequential analyses; worst-case scenario analyses; random-effects meta-regression.

INDEX TERMS

Medical Subject Headings (MeSH)

Disaccharides [adverse effects] [*therapeutic use]; Hepatic Encephalopathy [*drug therapy] [mortality] [*prevention & control]; Lactulose [*therapeutic use]; Liver Cirrhosis [*complications]; Neomycin [therapeutic use]; Randomized Controlled Trials as Topic; Sugar Alcohols [*therapeutic use]; Watchful Waiting

MeSH check words

Humans